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Proceedings Of The University of Toronto Undergraduate Medical Research Day

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MSRD
Medical Student Research Day

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PROGRAM

1:00-2:00 **Keynote Speaker: Dr. C. David Naylor**
"Evidence Based Medicine, An Idiosyncratic Perspective."
Room 3154, Medical Sciences Building

2:00-4:30 **Poster Viewing**
Stone Lobby, Medical Sciences Building

4:45-5:30 **Presentation by Winners of 1998 MSRD**
Room 3154, Medical Sciences Building

Danielle Gervais-Fagnou
Recipient of the George Brown Memorial Award – Clinical Research Category, Graduate Level, supervisor Paul Gross, Department of Medicine.
"Breast Cancer in Women Following Supradiaphragmatic Irradiation for Hodgkin's Disease."

Catherine Mason
Recipient of the George Brown Memorial Award – Basic Sciences or Clinical Research Category, MD/Ph.D Level, supervisor Marlene Rabinovitch, Department of Paediatrics.
"HVJ-Liposome Mediated Gene Transfer with a Plasmid Encoding Decoy RNA Containing the 3' Untranslated Regulatory Region (3'UTR) of Fibronectin (FN) mRNA Inhibits Neointimal Formation in the Ductus Arteriosus (DA)."

Gihane Wasfy
Recipient of the George Brown Memorial Award – Basic Sciences Research Category, Graduate Level, supervisor Linda Penn, Department of Medical Biophysics.
Characterizing the Molecular Mechanisms of Lavastatin-Induced Apoptosis."

5:30-5:40 **Raffle**

5:40 **Award Presentation and Wine and Cheese Reception**
Ruth Kurdyak Medical Alumni Lounge, Medical Sciences Building

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Keynote Speaker:
C. David Naylor, MD, DPhil

Senior Scientist and CEO Emeritus, Institute for
Clinical Evaluative Sciences
Professor of Medicine, University of Toronto

Dr. David Naylor graduated from the University of Toronto, Faculty of Medicine with scholarships in medicine, surgery and pacdiatrics, and later earned a D.Phil. at Oxford as a Rhodes Scholar, before training in general internal medicine at the University of Western Ontario. He returned to Toronto as a Medical Research Council of Canada Fellow and joined the faculty of the University of Toronto in 1988.

In 1991, Dr. Naylor developed the proposal for the Institute for Clinical Evaluative Sciences (ICES), a non-profit organization dedicated to conducting research that contributes to the effectiveness, quality and efficiency of health care in the province of Ontario. He served as the Institute's Chief Executive Officer from its inception in 1992 until June 1998. From 1990 to 1996 he also served as the inaugural director of the Clinical Epidemiology Unit and Research program at Sunnybrook & Women's College Health Sciences Centre.

As Professor of Medicine at the University of Toronto, Dr. Naylor holds cross appointments in several departments of the Faculty of Medicine, in the Graduate Faculty of Nursing and in the Institute of Medical Science. As well as contributing to many ICES research projects, he maintains an agenda of independently funded research in the area of cardiovascular disease with the support of the Medical Research Council (MRC) and the Heart and Stroke Foundation of Canada, and is currently a Senior Scientist of the MRC.

Dr. Naylor's work has led to co-authorship of over two hundred articles and editorials published in a wide variety of medical journals. He has also served on a variety of editorial boards including the British Medical Journal, the Journal of the American Medical Association and the Canadian Medical Association Journal.

As well as his academic commitments, Dr. Naylor has served on scientific advisory and policy committees, both provincially and nationally. He has been the recipient of several awards including the John Dinham Cottrell medal of the Royal Australasian College of Physicians, the Hamilton Maynard medal of the Medical Association of South Africa, the Quality Management of Medical Care award of the Ontario College of Physicians and Surgeons, and the G. Malcolm Brown award of the Royal College of Physicians and Surgeons of Canada. Recently, Dr. Naylor was awarded the MRC's 1998 Michael Smith Award for Excellence in Research.

Message from the Dean

Arnie Aberman, MD, FRCPC, Dean of Medicine

Welcome to the 1999 Annual Medical Student Research Day. This is an important day for our Faculty, because it provides an opportunity for our undergraduate medical students to showcase the wide spectrum of research projects they have completed, often during summer studentships with Faculty of Medicine supervisors. These projects range from basic science to clinical studies to community-based projects, exemplifying the many career pathways open to today's medical students.

Taking a research project from concept to completion provides undergraduates with a stimulating learning experience, giving them the opportunity to discover if they have the self-discipline, dedication and creative thinking required to be a successful investigator. As Dean, I am proud to say that many of our undergraduate medical students do have these qualities. Take a look at their research projects and you will see what I mean. Research is an important tradition in our faculty and we continue to be inspired by the impact that research has on the practice of medicine. It is my hope that many of the students involved in today's Medical Student Research Day will continue that tradition. Congratulations to all the participants - and many thanks to the Faculty members who made this year's event possible.

Arnie Aberman, MD, FRCPC
Dean, Faculty of Medicine

Message from the Vice-Dean

Andrew D. Baines, MD, Ph.D, FRCPC, Vice-Dean, Education

The Faculty of Medicine Undergraduate Medical Student Research Day provides an opportunity for students to display the results of their research. Each summer approximately 100 medical students receive scholarships through the Faculty of Medicine enabling them to work on projects in basic science laboratories and clinical investigative settings. Their research follows diverse paths from basic molecular biology to clinical outcomes and community health. Approximately 40% of the students who apply are funded and present their work on Research Day. Selection is based on scholarship and merit of the proposed research. Students in the MD/Ph.D. program also present their work at Medical Student Research Day. The top-rated students in the categories of basic and clinical research, receive an all-expense paid trip to the Annual Medical Student Research Forum (USA) in Galveston, Texas, in April, representing our Faculty. In addition the Department of Medicine supports the top-rated student (in either the clinical or basic science category), supervised by one of its members, to attend the same meeting.

Why do students wish to extend their professional training into the realm of biomedical research? There are many reasons including scientific curiosity and extension of previous engagement in research. More than 30% of students now entering Medicine at Toronto hold graduate degrees. Nonetheless for many of the students, whose abstracts are contained in this journal, their first taste of research came after they entered the medical program. All the research presented at Research Day has been carried out while students are enrolled in the undergraduate medical program or the MD/Ph.D. program. Many of these students have and will contribute to scientific papers published in peer-reviewed journals. Some will seek future career development as clinician-scientists, by entering graduate or post-graduate research programs during or after clinical specialty training. The Faculty of Medicine at the University of Toronto is a major focus of basic and clinical investigation in Canada. The 13th annual Medical Student Research Day shows how effectively our medical students take advantage of this rich learning environment.

Students participating in research day have taken time out of a demanding professional training program to prepare and present their posters. Health care professionals engaged in research are challenged to maintain a balance between clinical and investigative responsibilities. The students who participate in Research Day begin to experience this sometimes difficult, yet highly rewarding, duality. The posters displayed at the Research Day demonstrate the fruits of their self-discipline, dedication and creativity.

The students and Faculty are indebted to the Medical Student Committee who worked so hard and efficiently in the planning and preparation for Research Day, and to the corporate donors who have provided financial assistance.

Andrew D. Baines, MD, Ph.D, FRCPC
Vice-Dean, Education
for the Research Day Coordinating Committee

Acknowledgements

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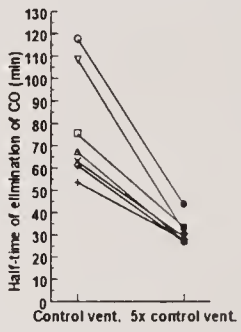
Anesthesia

AN1

ACCELERATED CLEARANCE OF CARBON MONOXIDE BY NORMOCAPNIC HYPERPNEA IN HUMAN SUBJECTS Rucker J.*, Takeuchi A., Vesley A., Tesler J., Sommer L., Lavine E., Fedorko L., Iscoe S., Fisher J. A. Dept. of Anaesthesia, Faculty of Medicine, University of Toronto

Background: CO elimination is accelerated by CO_2-stimulated ventilation in CO poisoned anaesthetized dogs. However, most conscious humans are unlikely to tolerate prolonged breathing of 5 – 10% CO_2. We propose to determine a) the effect of voluntary normocapnic hyperpnea on the rate of carboxyhemoglobin elimination and b) whether this normocapnic hyperpnea can be sustained for a duration sufficient to provide therapeutic benefit. **Methods**: After obtaining institutional board approval, seven normal male volunteers were exposed to CO until their venous carboxyhemoglobin concentrations ([COHb]) reached 10%. They then breathed 100% O_2 at resting ventilation or ~5 times resting (~ 96% O_2 balance CO_2) for 1.5 h on separate days. A non-rebreathing circuit (Eur.Respir. J.12(3):698.1998) was used to maintain normocapnia during hyperpnea. The half time ($t_{1/2}$) was calculated from plots of [COHb] *versus* time. **Results**: The $t_{1/2}$ fell from an average of 78 min during control ventilation to 31 min during hyperpnea. All subjects sustained the hyperpnea without difficulty. End tidal PCO_2 during hyperpnea did not change from that during exposure to CO. **Conclusion**: Sustainable normocapnic hyperpnea markedly reduces the $t_{1/2}$ of CO elimination. We suggest that normocarbic hyperpnea may provide an effective inexpensive pre- and in-hospital treatment option for CO poisoning.



Funded by the Nusbaum Foundation

Biochemistry

BC1

A CLINICAL PROTOCOL FOR MAGNETIC RESONANCE ANGIOGRAPHY OF THE LOWER EXTREMITY IN PERIPHERAL VASCULAR DISEASE. L. Nijmeh*, G. Kim, N. Merchant, P.G. Kalman, D.S. Kucey, G.A. Wright. Depts. of Medical Biophysics and Vascular Surgery, Sunnybrook Health Sciences Centre, The Toronto Hospital, University of Toronto.

Symptomatic lower extremity ischemia due to peripheral vascular disease (PVD) is a major cause of disability in Canada. Surgical intervention is via an arterial bypass. For such a surgical procedure, it is necessary to locate a suitable target vessel for the bypass taking into consideration such factors as patency of the vessel and the run-off from potential bypass sites. The current gold standard in imaging the arteries is x-ray contrast angiography. Due to slow flows in these vessels, x-ray angiography does not always provide accurate imaging as the contrast agent has difficulty reaching distal vessels. Furthermore, x-ray contrast studies are invasive, involve extended hospital stays and potential complications. Despite the risks and discomfort of x-ray angiography, it is capable of demonstrating the vasculature with sub-millimetre resolution. Magnetic resonance angiography (MRA) presents a fast, non-invasive method of visualizing the peripheral vasculature. After consultation with vascular surgeons from two academic hospitals, it was determined that accurate depiction of vessel anatomy from knee to ankle is most essential in surgical planning. Therefore, the aim of this study was to develop a clinical protocol for high resolution MRA imaging focused on this region with the goal of depicting outflow anatomy in a single scan. It was hypothesized that 3D gadolinium-enhanced (Gd) MRA would be the method most capable of providing high quality images in a short exam time. One healthy subject and three patients with PVD were studied with 3D Gd-MRA and 2D time-of-flight (TOF) MRA. All patients also had x-ray angiography as part of their surgical workup. Subjects were scanned with a 1.5 T GE Signa system and a torso coil, centered between the ankle and knee. Two vascular surgeons were consulted to interpret the images. 3D Gd-MRA was significantly faster in imaging the lower limb and the resulting image quality was clearly superior to that of 2D-TOF MRA. The studies also indicate that 3D Gd-MRA offers the same information as x-ray angiography. With improvements in coverage and timing, and a larger clinical study, 3D Gd-MRA may provide the information necessary for vascular surgery planning, eliminating the reliance on x-ray angiography.

BC2

ALTERNATIVE PATHWAYS OF MAP KINASE ACTIVATION BY TYROSINE KINASE RECEPTORS.

T. Tsakiridis, A. Bergman and G.P. Downey, Department of Medicine, Faculty of Medicine, University of Toronto

The extracellular signal regulated (Erk) MAP kinases are involved in the mediation of the nuclear effects of many cell surface receptors. The objective of the present studies was to investigate the mechanism of Erk activation by insulin, Insulin-like Growth Factor-I (IGF-I) and Platelet Derived Growth Factor (PDGF) in muscle cells. Insulin-activation of Erks is initiated by the tyrosine phosphorylation of the adaptor molecules Src and collagen homologous (Shc). Phosphorylated Shc binds the small adaptor protein Grb2 which, through the nucleotide exchange factor Sos, activates the small GTP binding protein Ras. Activated Ras can then induce Erk activation through the protein kinases Raf and MEK. Treatment of differentiated L6 muscle cells with cytochalasin D and latrunculin B, two structurally distinct actin-disrupting agents, abolished insulin-induced phosphorylation and activation of Erks indicating that an intact actin network is required for insulin-induced phosphorylation and activation of Erk. These two agents also inhibited insulin-induced activation of Ras and association of Shc with Grb2 without altering Shc phosphorylation, indicating an early requirement for an intact cytoskeleton in the initiation of the mitogenic cascade of insulin. Interestingly, actin disassembly did not alter Erk phosphorylation by either IGF-I or PDGF but was able to inhibit IGF-I-induced Ras activation. PKC inhibition by bisindolylmaleimide (10 uM) abolished PDGF but not IGF-I- or insulin-induced Erk activation. These results suggest that in muscle cells, at least three alternative pathways leading to Erk activation exist: i) a cytoskeleton- and Ras-dependent, PKC-independent, pathway utilized by insulin, ii) a PKC-dependent, cytoskeleton-independent pathway used by PDGF and iii) a cytoskeleton, Ras and PKC-independent pathway utilized by IGF-I. Financial Support: Medical Research Council of Canada

BC3

Cloning and functional characterization of NKIATRE, a novel kinase related to both MAPKs and cyclin-dependent kinases

R. Haq[1,4], S. Randall[3,4], M. Midmer[3,4], B. Iafrate[4] and B. Zanke[1,2,3,4] [1]MD/PhD Program, Department of Medicine, Institute of Medical Science, [2]Departments of Medicine and [3]Medical Biophysics, University of Toronto, and The Princess Margaret Hospital and [4]The Ontario Cancer Institute, Toronto, Ontario

Intracellular signaling cascades are manipulated by a range of extracellular stimuli resulting in diverse outcomes such as cell division, apoptosis and differentiation. Key to the cellular response to extracellular signals are the Mitogen-Activated Protein Kinases (MAPKs). To identify novel MAPKs, a degenerate PCR approach was undertaken. A 57 kDa protein kinase, termed NKIATRE, was molecularly cloned from a rat brain cDNA library. A distinct isoform of the same kinase was also isolated from jejunum. Like other MAPKs, NKIATRE has a Thr-Xaa-Tyr motif in the subdomain VIII. However, NKIATRE also shows homology to the cyclin-dependent kinase class of protein kinases, containing conserved inhibitory phosphorylation sites, and a putative cyclin-binding domain. NKIATRE is expressed predominately in differentiated tissues, and expression was not detected in all cell lines examined. Subcellular localization using green-fluorescence protein (GFP) fusions indicates that the rat brain isoform localizes to both the cytoplasm and nucleus, whereas the jejunum form is found only in the cytoplasm. In addition, sequence analysis identifies a sequence rich in proline, glutamic acid, serine and threonine amino acids (PEST) present only in the brain isoform. These PEST sequences are frequently found in rapidly degraded proteins. Biochemical characterization of the protein suggests that NKIATRE is activated following stimulation with epidermal growth factor (EGF), but activation does not require phosphorylation at the Thr-Xaa-Tyr motif. These results suggest that NKIATRE is regulated by a different mechanism compared to MAPKs. A clinical relevance to NKIATRE is suggested by the localization of a human homologue to 5q31.1, a site frequently mutated in acute leukemias and myelodysplastic syndrome.

Cardiovascular

CV1

Autologous Cardiomyocyte Transplantation Improved Infarcted Porcine Heart Function

Peter Kan, Adrian Harvey, Ren-Ke Li, Richard D. Weisel. Division of Cardiovascular Surgery, Department of Surgery, Faculty of Medicine, University of Toronto, Toronto.

Background. Cardiomyocyte transplantation improved function of damaged rat heart. However, allograft resulted in rejection and transplanted tissue decreased in size with time. Present study evaluated autologous cardiomyocytes transplantation on heart function of infarcted swine.

Methods. Myocardial infarction was generated by occluding the LAD of an adult swine at its distal third with a coil. Myocardial biopsies were obtained from septum for cell culture. At 4 weeks post infarction, gated SPECT was performed and the cultured cardiomyocytes (Tx, N=12) and culture medium (control, N=7) were transplanted into the scar tissue. At 4 weeks post transplantation, the SPECT was performed again and then ventricular pressure and volume were measured using Millar and conductance catheters respectively. Histological studies were also performed.

Results. Body weight of Tx swines were significantly greater ($p<0.01$)than control ones. SPECT data demonstrated that heart ejection fraction increased significantly at 4 weeks post transplantation compared to pre-transplantation. Regional perfusion, movement and thickness at post transplantation were greater than those at pre-transplantation in self-control study. Ventricular pressure and volume measurements showed that preload-recruitable stroke work and end-systolic elastance of Tx hearts were significantly greater than those of control hearts. Histological studies showed that the autotransplanted cardiomyocytes formed visible cardiac tissue within myocardial scar tissue. No rejection was observed at transplanted sites.

Conclusion. In adult swine model autologous cardiomyocyte transplantation improved infarcted heart function. The cardiomyocyte graft has induced angiogenesis and limited scar expansion. These data suggested that cell therapy could be a new technology to repair infarcted hearts.

CV2

ABSORPTION IN RATS OF PHENOLS PRESENT IN RED WINES. Mark P. Angelini*, Dr. D.M. Goldberg, Dr. E.P. Diamandis. Department of Laboratory Medicine and Pathobiology, Mount Sinai Hospital, University of Toronto, Canada.

It has been suggested that those who drink wine regularly exhibit lower mortality due to coronary heart disease (CHD) than those who consume other alcoholic beverages. Phenolic constituents in red wine, namely the trihydroxystilbene resveratrol, and the flavonols, quercetin and catechin, have been shown *in vitro* to inhibit both LDL oxidation and platelet aggregation, and thus may protect against the initiation and progression of atherosclerosis. There exists a paucity of data on the bioavailability of these phenolic compounds because most assay techniques are unable to provide reliable measurements of their concentrations in blood and urine. However, the recent availability of tritiated forms of resveratrol, quercetin, and catechin now renders such measurements feasible. Wistar rats were acclimated for at least seven days and were then administered, via gastric intubation, ^{3}H-resveratrol dissolved in either 10% ethanol, grape juice, or a homogenized puree of fruits and vegetables (V8). The rats were then fasted and kept in metabolic cages for 24 h for the collection of urine and stool. Following their sacrifice, the blood, urine and stool were assayed for ^{3}H content. From the radioactivity present in the urine, results suggest that absorption of resveratrol is highest from the V8 solution, with apparently no significant difference in resveratrol absorption between the 10% ethanol and grape juice solutions.

To determine whether the absorption of resveratrol includes a specific competitive-sensitive receptor, experiments were performed with co-administration of unlabeled and ^{3}H-resveratrol. There was no significant difference in the amount of radioactivity present in the urine upon varying the concentration of unlabeled resveratrol up to a maximum of 10^{-3}M. This suggests that either competition is not a feature of resveratrol absorption in the rat intestine, or that the mechanism is not saturable up to the highest concentrations that were employed. This hypothesis will be confirmed by competition experiments with catechin and quercetin which are structurally homologous to resveratrol.

CV3

EPIDEMIOLOGY OF KAWASAKI DISEASE IN ONTARIO, CANADA, 1995-1997 R. K. Han*, B. Sinclair, A. Newman, E. Silverman, B.W. McCrindle. The Hospital for Sick Children, University of Toronto, Canada.

Kawasaki disease (KD) is a systemic vasculitis of unknown etiology, and has become the leading cause of acquired heart disease in children, with coronary artery aneurysms occurring in up to 25% of untreated cases. To determine recent epidemiologic trends, we surveyed all hospitals and pediatric cardiologists in Ontario to identify cases of KD between 1995 and 1997. Overall response rate was 100% from hospitals. From 430 cases (81% typical KD), the annual incidence (per 100,000) by age was 14.5 in <5 yrs (with relative risk for males vs. females of 1.73), 4.1 in 5 to 9 yrs and 0.6 in 10 to 14 yrs. Relative risk by race (vs Caucasian) was Asian 5.1, Black 3 4, Hispanic 1.2 and other 1.9. There was a seasonal peak between November and February, with a smaller peak in June and July. Nearly all cases (96%) were admitted to hospital, with 93% treated with IVGG (94% treated within 10 days of fever onset, 10% received more than 1 dose). Coronary artery involvement included ectasia only in 27%, non-giant aneurysms in 9% and giant aneurysms (>8 mm) in 1.3%, with ventricular dysfunction noted in 2.6%. Aneurysms were noted in 6% of cases treated with IVGG within 10 days of fever onset, and 27% if treated later (p=0.001). Aneurysms were noted in 15% of cases <1 yr of age, 8% from 1 to 4 yrs, 6% from 5 to 9 yrs, and 17% from 10 to 14 yrs (p=0.21). Treatment delay (IVGG given after 10 days of fever) or no IVGG given was significantly related to age, and noted in 11% of patients <1 yr, 11% from 1 to 4 yrs, 17% from 5 to 9 yrs, and 39% from 10 to 14 yrs (p=0.02). After controlling for treatment delay or absence, age <1 year had the highest risk of aneurysms (odds ratio 3.34 relative to 5 to 9 yrs, p=0.05).

Conclusion: Epidemiologic trends are similar to previous studies in Ontario (1989-90, incidence 11.3 in <5 yrs). Diagnostic and treatment delays continue, with an associated increased risk of aneurysms.

CV4

ARM-ANKLE EXERCISE PRESSURE GRADIENTS IN ADULTS WITH COARCTATION OF THE AORTA

Sohal V. Goyal*, David A. Harrison, Gary D. Webb, Michael A. Gatzoulis. The Toronto Hospital, University of Toronto, Canada, M5G 2C4.

Background: Right arm hypertension and Doppler gradients are routinely used to identify patients with re-coarctation of the aorta (CoA). We examined the potential role of exercise arm-ankle pressure gradients (A-Ag) in improving the diagnostic accuracy of this complication.

Methods: Patients with previous CoA repair identified from The Toronto Congenital Cardiac Clinic for Adults database were invited to participate in the study. Clinical data, surgical records, echo, Doppler and exercising indices were all analyzed. Patients were divided into two groups based on peak exercise (pe) A-Ag.

Results: Thirty-six patients (21 male/ 15 female, age 29.9 ± 10.8 yrs, time from repair was 20.2 ± 10.6 yrs.) have participated in the study thus far. All patients were asymptomatic. Pe A-Ag ranged from -17 to 126 mmHg and correlated with resting right arm blood pressure (RAsBP, r=0.77, P<0.001), and pe RAsBP (r=0.66, P<0.001) but not with Doppler gradients at rest. Thirteen patients had a pe A-Ag ≥50 mmHg; age, sex and type of repair were not predictive of this subgroup.

	eA-Ag ≥ 50 mmHg	eA-Ag < 50 mmHg	P
Age at repair, yrs	7.9 ± 9.5	9.1 ± 8.8	0.74
RAsBP (rest), mmHg	132.3± 13.9	123.8 ± 19.1	0.19
A-Ag gradient (rest), mmHg	3.1 ± 6.3	-2.2 ± 9.3	0.09
Doppler gradient (rest), mmHg	21.3 ± 12.6	14.7 ± 12.7	0.20
LV mass (gm)	147.4 ± 56.4	173.1 ± 58.9	0.30
RAsBP (exercise), mmHg	198.9 ± 29.0	157.8 ± 37.9	0.003

Conclusions: There is a high prevalence of exercise induced A-Ag in adults after repair of CoA. This was not solely due to re-CoA. Thus, repaired CoA may have an effect on reactivity of the peripheral vascular bed.

CV5

IS ROUTINE PULMONARY ARTERY CATHETERIZATION REQUIRED IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFTING SURGERY? M Yudin, BSc*, G Djaiani, MD, M Hynninen, MD, J Karski MD, J You, BSc, J Carroll RN,DCH Cheng, MD. Department of Anesthesia,The Toronto Hospital, University of Toronto, Toronto, Canada

Introduction. We conducted a prospective observational clinical trial to clarify the frequency of PAC data requirements for clinical intervention and determine the incidence of modified patient management based on this data during surgery and in the immediate postoperative period.

Methods. After IRB approval 72 patients with preoperative left ventricular (LV) function grade 1-3 underwent coronary artery bypass grafting (CABG) surgery. Central venous pressure (CVP) was displayed at all times. The attending anesthesiologist and surgeon were blinded to numerical values of PAC. This was only revealed in the presence of at least two of the following criteria: systolic blood pressure (SBP) < 90mmHg^{-1}, CVP > 15mmHg^{-1}, urine output < 0.5ml.kg^{-1}.h^{-1}, pH < 7.35 / HCO^-_3 < 18mmol.L^{-1}, SaO_2 < 95% / FiO_2 > 0.8 or ST changes ± 2mm. Initial treatment consisted of administration of colloid challenge, phenylephrine and/or dopamine (5μ.kg.min^{-1}) If this failed to restore normal hemodynamics within 10min period a preliminary diagnosis and potential treatment plan was documented by attending anesthesiologist. Following this the numerical PAC data was obtained and actual treatment instituted.

Results. The PAC was unblinded in 9 patients due to suspicion of low cardiac output state(CI). The diagnosis was based on a low SBP/high CVP in 6 patients and low SBP/ST changes in 3 cases. Low CI was confirmed in 2 patients. The remaining 7 patients received further fluid challenges with ensuing elevation in SBP (table 1).

Table 1.

Number of patients [n]	LV 1 (n = 44)	LV 2 (n = 21)	LV 3 (n = 7)
PAC unblinded	6 (13%)	2 (9%)	1 (14%)
Low CI /Hypovolemia	1/5	1/1	0/1

Discussion. Information acquired from unblinding PAC data changed clinical management in 10% of patients. This did not appear to be related to patients preoperative LV function. Preliminary results of our study suggest that routine use of PAC for CABG patients with LV grade 1-3 it may not be warranted and can be delayed until the need arises.

CV6

Prolonged action potentials increase intracellular calcium transients and enhances contractility in Kv4.2 knock-down mice. Rajan Sah and Peter Backx

Prolongation of the action potential is a common finding of heart disease, typically as a result of a reduction in repolarizing K^+ currents. The transient outward current (Ito) is a major repolarizing potassium current produced by K^+ channel genes Kv4.2 and Kv4.3 in adult mouse and rat myocytes and is critical in determining action potential duration and profile. Transgenic mice overexpressing an N-terminal fragment of the Kv4.2 potassium channel gene which reduces Ito currents in a dominant-negative manner, show a reduction in Ito at 3-5 weeks of age and develop congestive heart failure between 10-20 weeks of age. Action potentials are prolonged in transgenic myocytes (APD90 = 17.5 ± 1.6 ms) when compared to littermate controls (APD90 = 87.9 ± 19 ms) reflecting a decrease in repolarizing Ito. Monophasic action potential recordings (MAP) of Langendorf perfused hearts confirmed isolated myocyte data by demonstrating a significant MAP prolongation globally in the intact left ventricles of transgenic mice (APD90 = 106.7 ± 6.3 ms) as compared to littermate controls (APD90 = 64.4 ± 2.5 ms). Intracellular calcium transients measured in Fura-2 loaded control myocytes revealed an increase from 0.71 ± 0.10 to 1.29 ± 0.26 in the 340/380 ratio when the myocyte was stimulated with a short control action potential versus a prolonged transgenic action potential respectively. Augmented calcium transients in control myocytes driven by transgenic action potentials demonstrates that a primary reduction in Ito and the resultant change in action potential duration and profile are sufficient to increase systolic and time averaged calcium levels in the myocyte. Indeed, hemodynamic measurements of early stage (3-5 week) transgenic mice show evidence of hypercontractility consistent with elevated systolic calcium. Our results suggest that a prolongation of myocyte action potential duration and MAP in transgenic mouse ventricles cause globally elevated calcium transients and increased contractility in early stage transgenic mice. It is possible that enhanced contractility and/or increased time averaged calcium levels may underlie the initiation of progression to hypertrophy and end-stage heart failure via stretch or calcium activated signaling pathways.

Clinical Pharmacology

CP1

CUTANEOUS ADVERSE DRUG REACTIONS TO TRIMETHOPRIM-SULFAMETHOXAZOLE IN HIV-INFECTED PATIENTS: REVIEW OF DATA FROM THE HIV ONTARIO OBSERVATIONAL DATABASE.

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Background. Antiretroviral agents and drugs used for management of opportunistic infections such as trimethoprim-sulfamethoxazole (TMP-SMX) are associated with high rates of adverse drug reactions (ADRs) in people living with the Human Immunodeficiency Virus (HIV).

Objective. To evaluate the utility of the HIV Ontario Observational Database (HOOD) for studying ADRs in HIV-infected patients using cutaneous reactions to TMP-SMX as a paradigm.

Methods. From a MEDLINE literature review and a chart review of the Sunnybrook HIV Clinic population, we identified demographic, clinical and laboratory data relevant to the study of TMP-SMX cutaneous reactions. We evaluated the HOOD for availability and utility of these variables. Data from the HOOD related to variables in our list were analyzed.

Results. From January 1995 to June 1998, 2394 patients from 12 adult tertiary care clinics enrolled in the HOOD. 1417 (59.2%) were exposed to TMP-SMX, 343 (24.2%) of whom experienced adverse reactions. The breakdown of TMP-SMX ADRs are as follows: rash (55.4%), fever (5.0%), internal organ involvement (2.3%), anaphylaxis type symptoms (1%), two or more of rash, fever, and/or internal organ involvement (17.5%), and 'allergic' reactions without more specific descriptions (9.3%). Patients who were on TMP-SMX for treatment of PCP were more likely to experience adverse reactions than those who used the drug for prophylaxis only (28.6% vs. 20.4%, χ^2=8.290, df=1, $p \leq 0.004$). One in five patients with cutaneous reactions continued using TMP-SMX. A significant number of patients with ADRs to TMP-SMX also reacted to other drugs used for PCP treatment and prophylaxis. In particular, 19.8% had ADRs to dapsone.

Conclusions. Although a significant amount of epidemiologic data was gained from HOOD, the utility of the database for studying risk factors for TMP-SMX ADRs other than the reason for TMP-SMX use was limited because relevant data on demographics, clinical history, and laboratory test results were not recorded. Ways to improve the HOOD for monitoring TMP-SMX and other ADRs were outlined.

CP2

HEALTH-RELATED UTILITY MEASUREMENTS IN TREATMENTS FOR SEVERE HEMOPHILIA A. NA Risebrough, PI Oh, V Naraine,* V Blanchette, S Lee, A Stain, D Hedden, JM Teitel, B Feldman. Sunnybrook Health Science Center, Hospital for Sick Children, St. Michael's Hospital, and the University of Toronto, Toronto, Canada.

Primary Factor VIII prophylaxis (PRO) in patients with hemophilia reduces bleeding, joint damage, and subsequent disability but has associated risks and unknown impact on overall quality of life. Objectives were to measure the utility values defined as patient preferences for hypothetical health scenarios related to no PRO (on-demand therapy (ODT)) and PRO with or without complications. Utilities are global, subjective values ranging from 0 (death) to 1 (perfect health). Using the Standard Gamble method, utility interviews were conducted with the general society (GS (n=30)), parents of hemophilic children (HP (n=30)), and adults with hemophilia (HA (n=28)). Scenarios based on clinical practice and published sources, included *(1)* ODT with infrequent joint bleeding (<3 in 3 months); *(2)* ODT with frequent joint bleeding (≥ 3 in 3 months), *(3)* PRO either 1 time/wk, 2 times/wk or 3 times/wk with reduced bleeding, *(4)* PRO requiring implanted vascular access (PORT), and *(5)* PRO with PORT infection. Results are presented below.

Health State Profiles		HP (N=29) Mean (SD)	HA (N=28) Mean (SD)	GS (N=30) Mean (SD)
Age		38.6 (7.4)	35.8 (10.8)	33.5 (10.9)
ODT	Infrequent bleeding	0.934 (0.102)	0.906 (0.107)	0.884 (0.103)
	Frequent bleeding	0.876 (0.123)*	0.870 (0.129)*,+	0.808 (0.156)*
PRO	1x/wk	0.952 (0.089)*	0.939 (0.097)*	0.934 (0.064)*
	2x/wk	0.958 (0.087)	0.935 (0.099)	0.933 (0.068)
	3x/wk	0.947 (0.120)+	0.923 (0.107)	0.931 (0.089)+
	3x/wk + PORT	0.900 (0.156)+	0.913 (0.104)+	0.882 (0.116)+
	3x/wk +PORT+ Infection	0.868 (0.185)	0.892 (0.115)	0.843 (0.143)

* + significant differences between profiles within populations (p<0.006 significant, Wilcoxin Ranked Sum Test)

In summary, *(1)* No difference was found in utility values of the three PRO regimens in all study populations. *(2)* PRO was significantly preferred to ODT in all three populations. *(3)* Requiring a PORT for PRO significantly reduced ratings in the GS and HP populations but not the HA. *(4)* Even when the PORT was required, PRO was still preferred to ODT in all study populations, but only reached statistical significance in the HA population. In conclusion, prophylaxis in hemophilia significantly improves quality of life as rated by general society, hemophiliac adults and parents of children with hemophilia.

Endocrinology

EN1

THE RELATIONSHIP BETWEEN ALBUMIN EXCRETION RATE AND CARDIAC AND BLOOD VESSEL DYSFUNCTION IN ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS. Amish Parikh*†, Anne Dipchand°, Jeffrey Smallhorn°, Brian McCrindle°, Arun Mohanta‡, Alan Daneman‡, Etienne Sochett† and Denis Daneman†. Divisions of Endocrinology†, Cardiology° and Diagnostic Imaging‡, Department of Paediatrics, The Hospital for Sick Children, Faculty of Medicine, Univ. of Toronto.

Introduction: Microalbuminuria [albumin excretion rate (AER) > 15 µg/min] is one of the earliest indicators of kidney involvement in diabetes. Studies in Type 1 and II microalbuminuric adult diabetics have shown impaired cardiac function, decreased carotid artery distensibility and compliance and increased carotid artery intimal-medial thickness (IMT) compared to controls and normoalbuminuric diabetic adults. However, very limited research has been done in the adolescent diabetic population.

Purpose: To compare cardiac function, carotid artery distensibility, compliance and IMT in adolescents with Type 1 diabetes (normoalbuminuric and microalbuminuric) and healthy non-diabetic controls. To also correlate these findings with body SA, serum lipids, blood pressure, duration of diabetes, HbA1c, daily insulin dosage and AER.

Hypothesis: Diabetes and more importantly, microalbuminuria, will be associated with impaired cardiac function, decreased carotid artery distensibility and compliance and increased IMT, suggesting a spectrum of risk for cardiovascular disease.

Study population: 48 adolescents aged 14 to 20 yrs (32 diabetics from Diabetes Clinic at HSC [19 males, 13 females] and 16 controls [7 males, 9 females]).

Data collection and analysis: Each participant had: (i) fasting blood (serum lipids), (ii) echocardiogram (systolic and diastolic function), (iii) ultrasound of right carotid artery 1cm proximal to bifurcation (IMT, distensibility, compliance) and (iv) 3 timed urine samples (AER). Once data collection is complete, groups will be compared looking for relationships between heart function, blood vessel properties and AER.

Future implications: If our hypothesis is correct, then the presence of microalbuminuria signals not only risk for nephropathy but progression of the macrovascular cascade. Therefore any interventions aimed at decreasing microalbuminuria should also assess macrovascular outcomes.

EN2

CYSTIC LESIONS OF THE PITUITARY: CLINICOPATHOLOGICAL FEATURES DISTINGUISHING CRANIOPHARYNGIOMAS, RATHKE'S CLEFT CYSTS, AND ARACHNOID CYSTS IN 53 ADULT PATIENTS.

J. L. Shin*, L.J. Woodhouse, S.L. Asa, H. S. Smyth, and S. Ezzat. Departments of Medicine, Neurosurgery, and Pathology, Faculty of Medicine, University of Toronto, Toronto, Canada.

Background: The distinction between craniopharyngiomas (CR), Rathke's cleft cysts (RCC), and intrasellar arachnoid cysts (AC) remains a difficult preoperative problem. Accurate diagnosis of these rare pituitary lesions from the more common pituitary adenomas is important to determine the type of treatment and predict prognostic outcome. **Objectives:** To investigate distinguishing preoperative clinical, biochemical, and radiographic features of patients with CR, RCC, and AC. **Methods:** Fifty three adult patients aged 37 ± 14 years included 28 patients (14M:14F) with CR, 23 patients (8M:15F) with RCC, and 2 patients (2F) with AC. Mean follow-up duration was 70 ± 96 months. Histopathologic analyses, clinical and operative notes, and radiographic investigations were reviewed. Statistical package for Social Sciences (SPSS) was utilized to compare CR and RCC with independent t-tests, Fisher exact test, and Pearson correlation coefficient. **Results:** Due to mass effects, CR usually presented with hormonal symptoms (89%), neurological deficits (61%), ophthalmologic problems (60.7%), and frequently also psychiatric manifestations (32%); RCC never had psychiatric manifestations (vs. 70% hormonal, 61% neurologic, 39% ophthalmologic symptoms). Only CR (52%) showed calcification on CT scans pre-operatively. CT cyst intensity distinguished CR (53% hypodense, 47% mixed density) from RCC (92% hypodense, 8% mixed density). Postoperative biochemical testing showed no improvement in any of the pituitary axes in 46% of CR; 61% of patients with RCC had improvement of at least 1 of 6 axes, but only a small proportion normalized in all 6 axes (17%CR, 6%RCC). While all the RCC and AC were intrasellar and were managed by a transsphenoidal neurosurgical approach, CR had different surgical interventions depending on location. The 53% that had suprasellar disease required transcranial surgery; recurrence positively correlated with extent of resection for CR. Recurrence rate was 54% for CR, 22% for RCC, and 0% for AC. While surgical intervention improved most neurological, ophthalmologic, and endocrine symptoms, galactorrhea in CR, oligomenorrhea in RCC, diabetes insipidus (in CR and RCC) did not improve or became worse postoperatively. **Conclusion.** We describe the largest clinical, biochemical, radiographic, and histologic series of adult patients with cystic disease of the sella turcica. Calcification or mixed density on CT scans and psychiatric symptoms characterize CR; low recurrence rate is a feature of RCC and AC; and preoperative diabetes insipidus help distinguish these cystic lesions from pituitary adenomas, which has direct implications for neurosurgical intervention over medical therapy.

Gastrointestinal

GI1

Intravenous Proton Pump Inhibitors and H_2-Receptor Antagonists for the Immediate Treatment of Acute Upper Gastrointestinal Hemorrhage- A Meta-analysis of Randomized Controlled Trials

A. Ghai*, G. Tomlinson, J. Bowen, C. Papoushek and A.S. Detsky. Department of Medicine, Mount Sinai Hospital, University of Toronto.

Background. Despite the lack of reliable evidence from individual randomized controlled trials, intravenous proton pump inhibitors (PPIs) and H_2-receptor antagonists (H_2RAs) are commonly used for the initial treatment of acute upper gastrointestinal (GI) hemorrhage. Therefore a meta-analysis was conducted to determine the total evidence for this treatment option.

Methods. A MEDLINE, EMBASE and IPA literature search and a manual review of article bibliographies were used to identify all randomized controlled trials comparing intravenous PPIs or H_2RAs with placebo. Collected studies were divided into two groups based on the method of treatment administration. Studies were labeled as being "primary" treatment models when intravenous H_2RAs or PPIs were directly compared with placebo. Studies were labeled "secondary" treatment models when both intravenous and oral therapies were compared to various control therapeutic strategies. To estimate a summary effect for the primary outcomes, odds ratios (OR) and their associated 95% confidence intervals (CI) were computed for the primary, secondary and combined study groups.

Results. Summary OR demonstrated a slight trend for a protective effect of acid reduction therapy for the continued bleeding and operation need outcomes in each of the study groups. A trend for a harmful effect of intravenous acid reduction therapy was noted for the mortality end point in the primary and combined study groups.

Study Groups	Continued Bleeding	Operation Need	Mortality
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Primary (8S)	0.859 (0.667 to 1.105)	0.817 (0.527 to 1.267)	1.336 (1.066 to 1.676)*
Secondary (17S)	0.762 (0.603 to 0.964)*	0.895 (0.685 to 1.170)	0.901 (0.627 to 1.294)
All Studies (25S)	0.807 (0.681 to 0.955)*	0.862 (0.693 to 1.073)	1.038 (0.803 to 1.343)

* $p < 0.05$, S- studies

Conclusion We conclude that the benefit derived from intravenous acid reduction therapies for patients who present with acute upper GI hemorrhage has not been established.

Health Care Delivery

HD1

PERCEPTION OF QUALITY OF LIFE OF PATIENTS WITH METASTATIC BREAST OR PROSTATE CANCER BY PATIENTS, THEIR PARTNERS OR CLOSE RELATIVES, AND THE TREATING PHYSICIAN. Kerry A. Wilson*, Anthony J. Dowling, Ian F. Tannock. Department of Medical Oncology and Haematology, Princess Margaret Hospital, University of Toronto, Canada, M5G 2M9.

Quality of life (QoL) is a major endpoint of palliative cancer therapy. Some patients are unwilling or unable to assess their own QoL. In such cases, it is not clear who can most accurately assess patient QoL. The purpose of this study was to determine possible differences in perception of QoL between patients with metastatic breast or prostate cancer, their spouse or close relative, and the treating physician. We hypothesized that physicians would perceive better QoL than patients, while close relatives would perceive worse QoL as compared to patients with metastatic breast or prostate cancer. Patients, a spouse or close relative, and the treating physician each completed the same QoL questionnaire indicating how each perceived the patient's QoL. Differences in scores between patients and physicians, and between patients and relatives were determined. For the patients with metastatic breast cancer we found that physicians tended to underestimate overall QoL, overall health, diarrhea, social functioning, and role functioning. Close relatives tended to overestimate pain and emotional impairment. For the patients with metastatic prostate cancer, physicians tended to underestimate pain and to overestimate strain on family relationships. Spouses of patients with prostate cancer gave concordant ratings on all QoL domains. We conclude that for both metastatic breast and prostate cancer, close relatives and physicians provide similar ratings as compared to patients for many QoL domains, however close relatives accurately assess QoL on more domains than physicians. Where possible, close relatives should be incorporated into management decisions regarding palliative therapy for patients with metastatic breast or prostate cancer.

HD2

SELF ERASING ERRORS AND MEDICAL DECISION MAKING. P. Aujla*, D. Redelmeier. Institute for Clinical Evaluative Sciences, Sunnybrook Hospital, 2075 Bayview Ave., Toronto, Canada, M4N-3M5.

We have examined the impact of the cognitive bias of self erasing error on the medical decision making process of physicians. The self erasing error we examined can be defined as a pattern of reasoning in which the effort of collecting irrelevant information is validated by including that information in subsequent decisions. We hypothesized that this cognitive bias, known to influence non-medical decision making, also influences physicians' decisions, such that clinically irrelevant information is more likely to be included in the decision making process if greater time and resources are required to collect that information. We used a survey with 2 formats to explore this hypothesis. Physicians were randomly assigned to one of the 2 formats. The surveys involved a clinical scenario for which the physicians were expected to offer a management decision from a list. The 2 formats differed in that a piece of clinical information was offered immediately in one version, while in the other version, the physicians were asked if they would actively choose to obtain that same piece of information, effectively increasing the effort required. There were 395 total respondents. Of those in the low effort group, the answers of 11.4% of respondents indicate influence by the key piece of information. Of those in the high effort group, 21.1% of respondents seem to have been influenced by the same piece of information. Of those in the high effort group who chose to pursue the piece of clinical data, 82% of the decisions are indicative of an influence by that piece of information. The results significantly ($p<0.01$) indicate the influence of self erasing errors on medical decision making. We conclude that physicians are more likely to include a piece of clinical information in the decision making process if greater time and resources were required to obtain that information.

HD3

HOSPITAL BED UTILIZATION: ADMISSIONS TO A EUROPEAN MEDICAL WARD SPECIALIZING IN DIABETES MELLITUS
A. Bugeja*, J. Azzopardi. Department of Medicine, St. Luke's Hospital, University of Malta, Europe.

It has been shown that 60% of admissions to the general medical wards of St. Luke's Hospital in Malta was for diabetes and its complications. The elucidation of factors affecting the extended length of stay (LOS) of patients in a general medical ward allows for the assessment of hospital care and targets ways to improve resource utilization in the treatment of diabetic patients. The special interest of the general medical ward studied is in Diabetes Mellitus). Inpatient data forms outlining the nature of the patients' admission for 160 discharged patients were completed. The average length of stay of patients on a general medical ward was 9.4 ± 0.9 days with a median of 7 days. 7.5% of patients had a LOS greater than 18 days and these patients occupied 34.46 percent of total bed days. This extended length of stay was largely due to patients with diabetic foot infection, social issues or neoplasm. The mean LOS of patients with a diabetic foot infection was 24 days ± 7.3 days with a median of 11 days. Patients with a diabetic foot infection occupied 11 % of bed days. The first and third quartiles were 9 and 39 respectively. A two-sample student's t-test showed a significant difference ($p<0.05$) between the average length of stay of patients with a diabetic foot infection and all other patients. These results suggest that alternative methods of resource utilization must be considered in the treatment of patients with a diabetic foot infection.

HD4

EVALUATION OF THE EFFECTIVENESS OF ART THERAPY IN TREATING VICTIMS OF TORTURE.
M.Antoniades*, C.Chalin, R.Meier. Department of Public Health Sciences, Faculty of Medicine, University of Toronto.

The objectives of this project were to explore the ways in which art therapy helps victims of torture overcome the negative effects of torture on their lives and to assess its effectiveness in doing so. Open-ended, semi-structured interviews were conducted with 9 CCVT clients who had taken part in the art therapy programme in the past. Several themes emerged from the participants' account of their experiences. Art therapy appeared to help participants communicate their painful experiences and express their emotions surrounding those experiences, sometimes to a degree which was surprising even to the participant themself. Two major factors contributed to this: (a)the process of creating art, which many felt facilitated expression more than the verbal or written. (b) The environment of safety, freedom and trust within which the art therapy was conducted. Functioning as a tool for introspection, art therapy also appears to have improved participants' understanding of themself and their situation, often leading to an improvement in self esteem and a more positive outlook towards the future. The participants' comments suggest that art therapy can have a significant role to play in helping victims of torture overcome the effects of their torture and move more confidently towards the future.

HD5

THE COST OF PALLIATIVE THERAPY WITH CPT-11 FOR ADVANCED COLORECTAL CANCER IN THE SETTING OF A PHASE II CLINICAL TRIAL.
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CPT-11 (Camptosar, Irinotecan) is a relatively novel chemotherapeutic agent that has exhibited therapeutic potential in the treatment of various malignancies including lung, ovarian, cervical, gastric and colorectal cancers as well as non-Hodgkin's lymphoma. To our knowledge, no published study to date has attempted to assess the costs of CPT-11 therapy in any setting. Using a detailed medical chart review and established methods of overhead cost allocation, we have described the cost of palliative CPT-11 therapy for advanced colorectal cancer in the setting of a phase II clinical trial from the perspective of the health care institution. A total of 40 patients were enrolled in the trial. The average cost per patient was estimated to be $14,500 Cdn for the duration of therapy (median 2 cycles) and approximately 54% of this amount was attributable to the cost of drug acquisition and preparation. Preliminary comparisons between the cost of CPT-11 therapy and other chemotherapies for advanced colorectal cancer suggest that CPT-11 is more expensive. However, the cost of CPT-11 therapy was shown to be comparable to the reported costs of palliative chemotherapy for some other common cancers.

Health in the Community

HC1

WOMEN WITH METATSTATIC BREAST CANCER: PERCEPTIONS OF PALLIATIVE CARE AND EXPERIENCE WITH METATSTATIC BREAST CANCER

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There has been little research directed towards investigating issues of palliative care (PC) from a patient perspective. A study was carried out using a qualitative design to identify the perceptions of women with metastatic breast cancer towards PC. Fifteen women diagnosed with metastatic breast cancer were recruited from the breast cancer clinics of Princess Margaret Hospital in Toronto. Using a semi-structured interview format, the following issues were explored with patients: understanding of their medical condition, meaning of PC, perceived benefits and drawbacks of PC, timing of its introduction to patients and acceptance of such care. Using a consensual approach, the study investigators identified two major groups of themes: PC and Experience with Metastatic Breast Cancer. Under the category of PC, themes revolved around the meaning of PC, evaluation of PC, information provision, end of life decision making and delivery of PC services. For Experience with Metastatic Breast Cancer, the themes included issues surrounding the disease progression, side effects of cancer and its treatment, coping, support, quality of care and hope. The results indicate that these women feel that information before PC is needed is important and that PC should begin when patients experience a functional decline. These results affirm the need for a paradigm shift away from the biomedical model to a needs based approach to the provision of PC.

HC2

HEALTH CARE NEEDS AMONG THE HOMELESS POPULATION THAT PRESENT TO EMERGENCY CARE FACILITIES T. Gill*, J. Spence, D.Cass, J.Richmond. Inner City Health Program, St. Michael's Hospital, Toronto, Ont.

Objective: To gather information about the medical, psychosocial and social issues regarding individuals that presented to the St. Michael's Hospital (SMH) Emergency Department (ED) without a fixed address.

Methods: A standardized data form was developed to collect information on demographics, education level, employment history, current living conditions, support systems, health care resources, and general health conditions of the homeless population. Interviews were conducted over a three week period to those that presented to the ED without a fixed address.

Results: Twenty-seven personal interviews were conducted during the study. The study participants were predominately male (70%), middle aged (median age 43) and lived in Toronto for greater than 5 years (55%) Overall, 41% were born in Toronto, 23% elsewhere in Ontario, and 25% in other areas of Canada. In regards to education levels, the majority had not graduated from high school (41%) and a significant number had not completed grade school (33%). Sixty-eight percent of the individuals declared themselves as out of the work force, which included not looking for work or unavailable to work. When the homeless were asked to identify any community support systems, 60% reported to have none, and only 30% reported to have either a case worker, shelter counselor, or social worker. Family support available was also rather devastating with 70% having no or poor family support, 7% with fair support, and 22% with excellent or good support. Results of the health care facilities accessed by the homeless indicated that 52% seek the medical attention at the ED, 30% at a walk-in clinic, and only 11% at a doctor's office. Of the people that chose the ED as their first choice, 60% of these individuals do not have a family doctor, and over half have visited the ED more than 10 times in the past year, many times for non-urgent health conditions.

Conclusion: Insight into a number of these issues regarding medical, psychosocial and social problems affecting the homeless population provide information to address health issues and the appropriateness of inpatient and outpatient care.

HC3

POPULAR PRESS COVERAGE OF CHRONIC FATIGUE SYNDROME. Phillip C. Shin*, Susan Abbey. Dept. of Psychiatry, The Toronto Hospital, University of Toronto, Canada, M5G 2C4.

Since its apparent emergence in the mid-1980s, Chronic fatigue syndrome (CFS) has received significant coverage in the North American popular press. Much of this coverage has focused on controversial aspects of the disorder, such as the uncertain and much disputed etiology of CFS. The expanding influence of the press in shaping public perceptions of health issues has compelled an analysis of the media's objectivity in these matters. Consequently, our study of CFS coverage in the popular press investigated the possibility of media bias in leading periodicals and newspapers in U.S. and Canada. The areas of etiology attribution, the doctor-patient relationship, attitudes toward psychiatry, and gender issues were analyzed both qualitatively and quantitatively via the use of NUDIST software and a standardized data collection sheet. Inter-rater reliability was established for data abstraction. Our preliminary qualitative results suggest a clear trend in the media toward generating newsworthy stories at the expense of objectivity. The organic etiology of CFS is overwhelmingly supported in popular press articles, despite growing acknowledgment by the medical establishment of CFS as a heterogeneous and multifactorial disorder. Furthermore, press coverage has consistently magnified conflicts between CFS patients and the health care profession, with a particularly negative portrayal of psychiatry. We propose that the popular press should provide more balanced coverage in its presentation of health issues to the lay public.

HC4

UNDERSTANDING SMOKING BEHAVIOR FROM A TEENAGE PERSPECTIVE THROUGH FOCUS GROUP DISCUSSION. A. GRILL*, P. CHART Preventive Oncology Program, Toronto Sunnybrook Regional Cancer Centre. Faculty of Medicine, University of Toronto

Smoking is regarded as Ontario's most important public health hazard. Twelve thousand people die annually as a result of cardiovascular disease, chronic obstructive pulmonary disease, and cancer related to tobacco use. It is estimated that 90% of smokers become addicted as teenagers, and several studies have shown that teenage smoking is associated with complex social problems including low levels of self esteem, motivation, and respect for authority. Despite the smoking prevention initiatives used to target this population, teenage smoking rates continue to increase. Understanding smoking behavior from a teenage perspective, therefore, is an important step towards generating successful smoking cessation initiatives.

In a collaborative effort between the Preventive Oncology Program at the Toronto-Sunnybrook Regional Cancer Centre and Southwood Secondary High School, a focus group interview involving teen-age smokers was conducted to examine opinions regarding tobacco use. The discussion was designed to recognize flaws in current smoking cessation programs, identify common risk factors influencing smoking behavior, and suggest new potential smoking cessation strategies. With further research efforts, these strategies may reduce the high morbidity and mortality levels of tobacco related disease in Canada, as well as address the complex social issues surrounding smoking behavior in teenagers.

We have shown that teenagers were dissatisfied with current smoking cessation programs. They ignore advertised health warnings, abstain from quitting programs offered at school, disregard parental advice, and obstruct legislation designed to prevent tobacco purchase. In addition, teenagers reported nicotine addiction, peer pressure, and boredom as the main risk factors influencing smoking behavior. Finally, increasing the cost of cigarettes was suggested as the strategy most likely to significantly decrease smoking activity.

HC5

WORK-RELATED DIFFICULTIES IN PATIENTS AFFECTED WITH RETINITIS PIGMENTOSA: EVALUATION AND GUIDELINES.

Najwa Esmail*, Robin Thackray, Alex V. Levin, Elise Heon.
Department of Ophthalmology, The Hospital for Sick Children, University of Toronto, Toronto, Canada.

BACKGROUND: In 1986, more than 450,000 Canadians were registered as blind or visually impaired, of which 174,460 (39%) were in their working years. Of the visually impaired population, only 33% of those who were of working age actively participated in the labor force, compared with 75% of the non-disabled working age population. Significant socioeconomic consequences are imposed on affected individuals with a mean reduction in work capacity of 86%.

PURPOSE: **(1)** To assess the knowledge of patients with RP on legislation detailing their rights and responsibilities concerning the impact of their visual impairment in the workplace. **(2)** To identify factors that lead to employment-related difficulties and discrimination in the workplace experienced by visually impaired individuals affected with RP. **(3)** To identify supportive resources for patients experiencing difficulties in the workplace because of their visual impairment.

METHOD: A survey was designed to investigate: (1) the impact of the visual impairment on employment, (2) the openness of the patients towards their employer about their disease, (3) the level of knowledge regarding legal rights, (4) areas where better information was required for the employees and the employer. Patients of the Eye Gene Team were recruited for this study.

RESULTS: Twenty patients affected with RP participated in the interview; two of these were employers. Eighty-percent of patients had experienced work-related difficulties and these were proportional to the visual impairment; 65% had been treated unfairly by their employer; 47% did not communicate their disability needs to their employer; and 90% were misinformed about their rights and responsibilities in the workplace.

CONCLUSION: Based on the findings, relevant legislation has been clarified in order to formulate guidelines and make recommendations detailing legal rights and options for recourse available to individuals facing employment-related difficulties.

HC6

An Algorithm to Evaluate Web Site Quality and Its Application to Prenatal Content on the World Wide Web

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Objectives: To develop criteria for patients to use to evaluate the quality of Internet health related web sites. In addition, to identify prenatal diagnoses and pregnancy related web sites that satisfied the criteria as a high quality web site.

Study Design: Using Medline and the Internet, a literature search was performed to identify systems that evaluate Internet health related web sites. Using this information, a set of criteria was developed to assist patients in evaluating the quality of information obtained from an Internet site. Using different search engines (AltaVista, Excite, HotBot, InfoSeek, Lycos, and Yahoo), 26 pregnancy related topics and prenatal diagnoses were explored on the Internet. The set of criteria was used to identify high quality web sites.

Results: There is a great deal of literature written on how to evaluate the quality of Internet health related web sites. However, many of the existing evaluation schemes are vague, complex, and are specifically designed for health care professionals. We created a set of 10 criteria for patients. The criteria include questions on accuracy, objectivity, authorship, currency, and design of the web site. The evaluation criteria was applied to 26 prenatal diagnosis and pregnancy related topics. Web sites were book-marked only if they satisfied the criteria as a high quality site. Identified web sites will soon be made available to patients through the Fetal Diagnosis and Treatment Centre web site.

Conclusions: The Internet is a rapidly growing medium of communication and education. Today, patients want to be informed about health care issues, and many use the Internet for this purpose. Since the web sites are uncensored, the greatest barrier to using the Internet is being able to identify reliable and accurate information. The evaluation criteria developed in this study will provide patients with a tool to decipher between high and low quality web sites. The goal of this project is to help patients maximize the benefits of the Internet and to reduce the risk of obtaining incorrect information from dubious web sites.

HC7

COPING BEHAVIOUR AND SOCIAL SUPPORT CONTRIBUTE TO HIGHER QUALITY OF LIFE AFTER SURGERY FOR INFLAMMATORY BOWEL DISEASE, **David. N. Moskovitz*, Robert. G. Maunder, Zane. Cohen, Robin. S. McLeod, Helen. MacRae. Division of General Surgery, Department of Surgery, Faculty of Medicine, Mount Sinai Hospital, University of Toronto, Canada. M5G 1X5**

The purpose of this study is to examine the association of coping behaviour at the time of surgery with IBD-related quality of life after surgery We also investigated the relationship of perceived social support to coping style and to post-surgical quality of life. Finally, the value of two instruments measuring these factors for pre-operative screening was assessed. **Methods.** Repeated measures multivariate analysis of variance of the 8 Ways of Coping (WOC) subscales between groups with high Inflammatory Bowel Disease Questionnaire (IBDQ) (IBDQ > mean) and low IBDQ (IBDQ < mean) was used to determine if a significant association of coping to quality of life (IBDQ) was present. Stepwise linear regression analysis was then used to determine the independent contribution of (1) current IBD-symptoms, (2) current perceived social support, and (3) the identified coping behaviours (self-control, self-blame, and escape, summed as a single index named maladaptive coping) to post-surgical quality of life . **Results.** MANOVA found a significant association between WOC scales and high or low IBDQ ($F = 4.77$, significance of $F < 0.001$). The lower quality of life group distinguishes itself by more frequent use of these maladaptive behavioural styles: self-control, self-blame, and escape. Regression analysis reveals that current IBD-related symptoms, current perceived social support and maladaptive coping behaviours at the time of surgery each make a highly significant independent contribution to post-surgical quality of life. The sensitivity of the MOS-SSS in identifying patients with poor post-surgical quality of life is 85% and the specificity 76%. The negative predictive value was 94%. If maladaptive coping is identified by WOC in subjects with low MOS-SSS scores, the specificity of the combined test is 91%, and the positive predictive value of the combined test is 68% **Conclusion.** The results of this study indicate that post-operative inflammatory bowel disease patients with higher health related quality of life use maladaptive coping less frequently and report more social support.

HC8

OBTAINING ONTARIO RESOURCE UTILIZATION COSTS FROM A GENERIC RESOURCE UTILIZATION QUESTIONNAIRE UTILIZED IN CLINICAL TRIALS.

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Introduction: Measurement of resource utilization is increasingly becoming part of multicenter clinical trials because of the need to provide economic arguments for therapeutic agents. The costs for these resource utilizations, however, should be obtained from local sources since they generally differ between specific jurisdictions.

Objective: To document how Ontario costs may be derived from generic measures of resource utilization and to document compatibility between these measures and local data sources.

Methods: Patients from a large multicenter trial were asked to answer questions concerning their out-of-pocket medical and non-medical expenses related to their disease or the drug they were taking. They were asked to provide information on visits to health professionals and healthcare institutions as well as the medical procedures they received. Additionally, patients provided estimates of the amount of work and leisure time lost by them or their caregivers due to their disease or therapeutic agent. The data obtained were translated into Ontario cost estimates by referring to the Ontario Health Insurance Plan Schedule of Benefits, Canadian census data on average yearly wages by age and gender, and a local Ontario hospital's costing system.

Results: The original questionnaire was not adequate to fully cost out the information provided. Hospitalization costs could be obtained for 81 % of the patients hospitalized during the 1998 fiscal year. Inaccuracies in the wording of the questionnaire and the type of questions asked were addressed in the design of a new resource utilization questionnaire to be used in future clinical trials.

Conclusions: The detailed levels of information required for the measurement of resource utilization could best be addressed by a questionnaire with open-ended questions for the patients' clinical problems. Coding may then proceed by using the Case Mix Group coding methodology published by the Canadian Institute for Health Information. A revised questionnaire is presented incorporating the necessary changes.

HC9

THE DIAGNOSTIC AND TREATMENT MODEL, A NEW PROACTIVE PARADIGM FOR ANALYZING AND MANAGING RAGE AND OTHER FORMS OF MALADAPTIVE BEHAVIOUR. C. Stemerdink*, S Homatidis, J E Huggins Don Mills – Eglinton Medical Centre, Toronto and Kerry's Place Autism Services, Aurora

We have shown that the Diagnostic and Treatment (D&T) Model is an effective algorithm for managing the aggressive and maladaptive behaviours often associated with autism The D&T Model is a behaviourally analytical paradigm which is clinically driven based on the presentation of the maladaptive behaviours It identifies several key and multi-layered components that contribute in varying degrees to the pathogenesis of such behaviours. It then offers a poly-therapeutic approach through limited medication and cognitive behavioural strategies in order to stabilise these components An evaluation of the efficacy of the D&T Model was accomplished through data collection from a questionnaire The questionnaire was sent to applicable family members and/or group home staff in order to gain feedback following the patient's assessment and treatment via the D&T Model. Interviews with the patient's family and/or group home staff were also conducted in order to complement the questionnaire. With full implementation of the D&T recommendations, family members and group home staff reported significant reduction in aggression to others, self (self-injurious behaviour) and to property Improvement was also reported in many areas of daily functioning Social interactions were more pleasant, the patient's performance at school or work placement if applicable had shown improvement, there was an increase in concentration and focus in every day tasks and there was a general improvement and/or increase in the patient's range of interests An area not showing consistent improvement was in respect to ease or difficulty encountered in redirecting the patient to a more productive activity The D&T Model provides an effective way to identify, sort out and manage complex behaviour patterns in individuals with autism

Hematology

HM1

OPTICAL TRAPPING AND MANIPULATION OF SINGLE RED BLOOD CELLS: TOWARD THE DEVELOPMENT OF AN AUTOMATED SINGLE CELL SORTING SYSTEM. S.C. Grover*, A.G. Skirtach[1], R.C. Gauthier[2], C.P. Grover[1]. *M.D. Student, Faculty of Medicine, University of Toronto, 1 King's College Circle, Toronto, Ontario, M5S 1A8; [1] Institute for National Measurement Standards, National Research Council, Ottawa, Ontario, Canada, K1A 0R6; [2] Department of Physics and Astronomy, Laurentian University, Ramsay Lake Road, Sudbury, Ontario, P3E 2C6.

We provide a basis for automated single cell sorting based on single and dual beam optical trapping using human peripheral blood as a model system. Theoretical analysis of the behaviour of a trapped red blood cell shows that it orients with its longest axis in the direction of propagation of the beam(s); this has been confirmed with experimental results. The automated single cell sorting system includes an image processing system which has been developed for the automated identification of single cells, allowing for subsequent automated manipulation and sorting by single and dual beam optical trapping. The dual beam optical trapping configuration is shown to be preferred due to a lesser photodamage to trapped cells and a greater ability to manipulate cells in three dimensions. Red blood cells have been successfully manipulated for distances greater than 1 mm and for times longer than 20 minutes using the automated dual beam trap, without morphologically visible photodamage. Potential applications of automated single cell sorting including the incorporation of molecular biology techniques are discussed.

HM2

NATURAL HISTORY OF PROGRESSION OF HEPATIC FIBROSIS IN PATIENTS WITH THALASSEMIA AND HEPATITIS C S.H.M. Yiu*, S. Sharma, N.F. Olivieri
The Hospital For Sick Children and The Toronto Hospital, General Division

Infection with Hepatitis C virus (HCV) accounts for more than 90% of transfusion-related hepatitis. In patients (pts) with β-thalassemia, iron overload contributes to chronic hepatitis, cirrhosis and in some pts, hepatocellular carcinoma. To date, no study has assessed the natural history of HCV infection in pts with β-thalassemia and iron overload. The mean rate of progression of fibrosis (defined as the ratio of fibrosis stage in Knodell units to the duration of infection) in HCV infected, non-thalassemic pts is reported as 0.133 (*Lancet, 1997: 349:825-32*). The contribution of HCV to fibrosis and cirrhosis in a population of iron loaded pts is presently unclear. We have retrospectively analyzed liver histology in a cohort of pts receiving transfusions and chelation therapy in Toronto (n=124). All patients who had undergone two or more liver biopsies, scored at the time of this writing, were included in this analysis (n=42; 19F, 23M); HCV positive (+ve) (n=23), or negative (-ve) (n=19), by ELISA. Liver histology was scored independently by two hepatic pathologists using the Knodell scoring system (*Hepatology, 1981:1:431-5*). The HCV +ve pts, aged 26.8 ± 1.4 (range 12-37) years were significantly ($p < 0.001$) older than the -ve pts (20.9 ± 0.8, range 15-30) years. Mean rate of progression of fibrosis was 0.109 ± 0.852 (range -2.959 - +1.886) in HCV +ve pts; and -0.112 ± 0.544 (range -1.901 - +0.721) ($p=0.29$) in HCV -ve pts. Over this time period, hepatic iron concentration (HIC) in HCV +ve pts did not significantly change, initial value 11.9 ± 2.1 mg iron/gram liver dry weight; final value 11.9 ± 8.4 mg iron/gram liver dry weight; ($p=1.0$). By contrast, in the HCV -ve pts, the HIC values changed significantly, initial value 9.5 ± 2.8 mg iron/gram liver dry weight; final value 15.1 ± 6.9 mg iron/gram liver dry weight; ($p=0.005$). In summary, in this small cohort of patients, hepatic iron did not appear to aggravate the progression of hepatic fibrosis in HCV +ve pts or in HCV -ve pts, in whom no progression of fibrosis was seen despite a significant increase in HIC. In our HCV +ve pts, in whom HIC had stabilized over this period, progression of fibrosis was similar to that previously observed in HCV +ve non iron-loaded pts (*Lancet, 1997: 349:825-32*), suggesting that iron may not play a substantial role in progression of fibrosis. These early findings need confirmation in a larger series, work is presently ongoing in this centre.

HM3

PREVALENCE OF BONE DISEASE IN IRON-LOADED PATIENTS. B. Hum*, R. Shaheen, N. Olivieri. Department of Hematology/Oncology, The Toronto Hospital, General Division and The Hospital for Sick Children, Faculty of Medicine, University of Toronto, Canada, M5G 1X8.

The thalassemias are the most common single gene disorders in the world, and complications of these diseases impact on thousands of patients in emerging countries. Osteopenia and osteoporosis commonly complicate beta-thalassemia secondary to medullary expansion, secondary hypogonadism, interference of iron with osteoblast formation, iron-induced hypoparathyroidism and compromised nutritional status. We studied a cohort of 65 patients (35 males: 30 females) with severe beta-thalassemia or Diamond Blackfan Anemia, aged 27.3 ± 8.0 (range:17-60) years to assess risk factors for bone disease, including gender, age, ethnic background, family history, smoking, alcohol and caffeine consumption, diet, calcium and vitamin D supplementation, hormone replacement therapy, weight-bearing exercise habits, bone pain, limitations of activity and history of fractures. All patients underwent quantitative digital radiography of bone mineral content and density of the femoral neck and lumbar spine. Osteopenia was defined as a density of 1 to 2.5 SD below the mean T-score for age, and osteoporosis was defined as a density of ≥2.5 SD below the mean (WHO, 1994). The majority (51%) of the patients were noted to have osteoporosis (n=33/65), while 38% were osteopenic (25/65). Mean T-score (± SD) was -2.31 ± 1.32 in the lumbar spine and -1.91 ± 1.05 in the femoral neck. A total of 52% of patients had a history of fractures, 57% had bone pain and 58% had limitation of activity. The precipitating factors of bone pain included inactivity, exertion, cold and humidity. These data demonstrate that transfusion-dependent patients have a strikingly high prevalence of osteopenia and osteoporosis which, because of improved survival to the fourth decade in these patients in the 1990s, represent an important problem of management affecting thousands of patients worldwide. This survey will form the basis of therapeutic trials of calcium, vitamin D and hormone replacement therapy to evaluate improvement of bone density with these therapies in patients with this common hemoglobinopathy.

HM4

DECISION ANALYSIS - A COMPARISON OF BONE MARROW TRANSPLANTATION VERSUS CONVENTIONAL TRANSFUSION-CHELATION THERAPY IN PATIENTS WITH HOMOZYGOUS ß-THALASSEMIA. S. Amlani*, M. Carcao, Division of Clinical Epidemiology, The Toronto Hospital, University of Toronto, Canada.

Bone marrow transplantation (BMT) offers a potential cure for the patient with thalassemia major, however is associated with a high rate of early mortality. Under conventional transfusion-chelation therapy these patients would otherwise face a progressive deterioration in health as a result of iron-induced organ damage along with a reduction in quality of life from the side effects and burden of chronic transfusions and iron chelation. The decision analysis method was used to compare these two branches of therapy on life expectancy (LE) and quality-adjusted life-years (QALY). An extensive literature review was conducted to derive probabilities of disease states associated with both arms of the decision analysis. Utility measures for QALY's were determined using the time-tradeoff method. Results are pending. We hypothesize that BMT will provide a better LE and QALY profile, but that these results will be highly sensitive to changes in mortality and rejection associated with transplantation. Also, improving chelation therapies will likely decrease complications of conventional therapy thereby improving quality of life and favoring this option of management.

Immunology

IM1

EPSTEIN-BARR VIRUS AND THE PATHOGENESIS OF MULTIPLE SCLEROSIS: ANTIBODY LEVELS TO EPSTEIN-BARR VIRUS AND OTHER HERPESVIRUSES IN MULTIPLE SCLEROSIS PATIENTS. D.B. Baryshnik*, P. O'Connor. Division of Neurology, St. Michael's Hospital, University of Toronto, Canada, M5B 1W8.

Objective – To evaluate the role of Epstein-Barr virus (EBV) in the pathogenesis of multiple sclerosis (MS), levels of anti-EBV antibodies were measured in MS patients in relapse and MS patients not in relapse. *Materials and methods* - Serum samples were collected from 13 MS patients in relapse and 26 MS patients not in relapse. Samples were analyzed via standard assays for anti-EBV antibodies (VCA IgM, VCA IgG, EBNA IgG, EA IgG), anti-varicella zoster virus (VZV) antibodies (IgG and IgM) and anti-herpes simplex virus (HSV) antibodies (IgG). Optical densities (OD) were obtained to reflect antibody levels. *Results* – If EBV plays a role in relapses of MS, anti-EBV antibody levels (OD) will be higher in MS patients in relapse as compared to MS patients not in relapse. We expect no difference in anti-VZV and anti-HSV antibody levels. *Conclusion* – Results of this study will help clarify the role of EBV in MS relapse.

IM2

POST-TRANSCRIPTIONAL REGULATION OF TUMOR NECROSIS FACTOR-α BY INTERLEUKIN-10 IN A MOUSE MACROPHAGE CELL LINE. G. Thanassoulis*, K. Matouk, D. Radzioch. Center for the Study of Host Resistance, Montreal General Hospital Research Institute, McGill University, Montreal, Quebec, Canada, H3G 1A4

Inflammation is a tightly regulated process that is mediated by pro- and anti-inflammatory cytokines. When there is an imbalance of these cytokines, a number of inflammatory conditions may ensue. In order to further understand the nature of this balance at a molecular level, the post-transcriptional regulation of Tumor Necrosis Factor-α (TNF-α) by Interleukin-10 (IL-10) was examined in cultured mouse macrophages. IL-10 inhibited TNF-α production optimally at 100U/mL when IL-10 was added simultaneously with the stimuli. Pretreatment of cells with IL-10 (100U/mL) for 1 hr and 2 hrs was shown to be less effective at inhibiting the production of TNF-α from macrophages stimulated with LPS (100ng/mL) or LPS+IFN (100ng/mL, 100U/mL, respectively). In order to elucidate the mechanisms of the IL-10 mediated inhibition of TNF-α, we examined TNF-α protein and mRNA levels. From these experiments we showed that when LPS was the inflammatory stimulus, IL-10 inhibited TNF-α production at 3 and 12 hrs by reducing transcription. When LPS+IFN was the inflammatory stimulus, IL-10 inhibited TNF-α production at 3hrs also by reducing transcription. However, at 12 hrs with LPS+IFN, IL-10 destabilized TNF-α mRNA and prevented the formation of complex B on the 3'UTR of TNF-α mRNA. These results suggest that IL-10 regulates TNF-α by different mechanisms depending on the strength of the inflammatory stimulus. Experiments to examine these effects of IL-10 on translation of TNF-α mRNA are ongoing . In sum, these studies provide molecular evidence that IL-10 is a crucial regulator of TNF-α and may provide insights into the pathogenesis and treatment of inflammatory conditions.

IM3

ALTERED INTERFERON GAMMA SECRETION BY PERIPHERAL BLOOD T CELL SUBSETS IN DIFFERENT DISEASE PHASES OF MULTIPLE SCLEROSIS P. S. Giacomini*, B. Becher, D. Pelletier, A. Prat, E. McCrea, and J.P. Antel. Neuroimmunology Unit, Montreal Neurological Institute, McGill University, Canada, H3A2B4.

Interferon gamma (IFN γ) is a pleiotropic cytokine which has been implicated as both an immune effector and regulator in the pathogenesis of multiple sclerosis (MS). Using flow cytometry coupled with intracellular cytokine staining, we compared IFN γ production by immediately *ex vivo* peripheral T cells from control subjects with those from untreated patients with relapsing remitting MS (RR) and secondary progressive MS (SP) as well as RR patients receiving IFN β therapy (IFNβ). Our results indicate that the SP group had an increased number of IFN γ secreting cells, whereas the RR group showed a reduction in IFN γ expressing cells, when compared to the control group. The IFN β treated patients showed an even greater reduction in IFN γ expressing cells relative to the control group. The increased expression seen in the SP group could reflect increased pro-inflammatory (Th1) cytokine activity in disease transition. However, considering that IFN γ has recently been shown to inhibit disease in mice with experimental autoimmune encephalomyelitis (EAE), the animal model for MS, the decreased expression of IFN γ in the RR group may be a factor contributing to disease susceptibility.

IM4

TWO DIFFERENT HIV-1 REVERSE TRANSCRIPTASE PEPTIDE-SPECIFIC CTL TARGET STRUCTURES. C. Dela Cruz*, R. Kim, S. Rowland-Jones and B. Barber. Institute of Medical Science, Dept. of Immunology, Faculty of Medicine, University of Toronto, Ontario, Canada.

We have previously shown that by immunizing C57BL/6 mice and HLA-B27 transgenic mice with plasmid DNA vector encoding a defined human class I MHC gene product, the human leukocyte antigen, HLA-A2, it is possible to induce both xenogeneic and allogeneic anti-HLA-A2 antibody and cytotoxic T lymphocyte (CTL) responses. Such anti-MHC immune responses could prove to be beneficial in humans in a viral antigen-independent vaccine approach against HIV, as strongly suggested by studies in SIV macaque models and with HIV-resistant Nairobi prostitutes. Since MHC molecules are already being used as plasmid DNA immunogens in this anti-HIV-1 vaccine strategy, we report here the creation of HIV-1 epitope-specific CTL targets by including HIV-1 reverse transcriptase (RT) epitope sequences in the HLA-A2 DNA constructs using two different strategies. Two 9-amino acid HIV-1 RT epitopes (pol346-354 & pol476-484) that are known to bind to HLA-A2 and trigger favourable anti-HIV CTL activity in patients are studied. Eliciting a strong CTL response depends upon displaying high levels of specific class I MHC-peptide complexes at the cell surface. Thus, in one strategy, the RT peptide epitope was used to replace the first 9 amino acids of the signal sequence peptide of the HLA-A2 gene., in order to develop an MHC-peptide coupled system by linking the biosynthesis and ER translocation of the HLA-A2 heavy chain and the RT antigenic peptide. In a second strategy, the RT epitope was physically linked to the HLA-A2 molecule by tethering the epitope to the heavy chain by a 10 aa linker sequence to enhance the immunogenicity of the RT peptide by increasing the physical association of the RT peptide with the HLA-A2 molecules. Using a multistep PCR-based approach, these epitope-containing HLA-A2 molecules were constructed. Transient COS-7 transfectants of the different constructs showed surface expression of conformationally intact HLA-A2 molecules as detected by HB82, an anti-HLA-A2 antibody, by flow cytometry. Differently-modified HLA-A2 G418-resistant stable transfectants of C1R human B lymphoblastoid cells similarly showed HLA-A2 expression on the cell surface. The C1R cells transfected with these HIV epitope-HLA-A2 fusion constructs (the signal sequence version or the linker version) were as effective, if not better than target cells expressing only the HLA-A2 molecule given exogenously pulsed peptides, in being sensitized *in vitro* for recognition and lysis by human HLA-A2-restricted HIV-reactive CD8+ CTLs (dervied from HIV-1 patients) that are specific for the RT epitopes. Thus, incorporating optimal HIV epitopes into the signal sequence of HLA or tethering epitopes to the HLA-A2 heavy chain provide simple methods for augmenting the biological activity of the peptides and for creating CTL target structures. This offers new options in the design of peptide-based vaccines or immunotherapeutics for patients with HIV.

IM5

Cloning and characterization of protein tyrosine phosphatases expressed in human neutrophils

J Kruger, Q Dong, T Fukushima, GP Downey
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Neutrophils (PMN) are important in host defense and, in pathologic circumstances, may mediate inflammatory tissue injury. Tyrosine phosphorylation is a key process which regulates many signaling pathways involved in PMN activation. Net tyrosine phosphorylation is the result of a balance between the activity of protein tyrosine kinases (PTK) and protein tyrosine phosphatases (PTP). Relative to PTK, little is known about the identity and functional importance of leukocyte PTP. Our goal was to clone and characterize PTP expressed in human peripheral blood PMN. A reverse transcriptase PCR cloning strategy was employed with degenerate primers based on highly conserved motifs in the catalytic domain of PTP. Using this technique, 5 PTP were cloned from total RNA including PTP1C, CD45, PTP1B, MEG2 and PTPε. Expression of PTP1C and CD45 in PMN has already been documented. Western blotting with commercially available antibodies confirmed the expression of protein for PTP1B in PMN. Polyclonal antibody against a MEG2 fusion protein was raised in rabbits and detected an immunoreactive band of the predicted molecular weight in PMN lysates. Phosphatase activity was confirmed for PTP1B and MEG2 and their subcellular localization was found to be cytoplasmic. Our results indicate that in addition to CD45 and PTP1C, peripheral blood PMN express supplementary PTP including PTP1B, and MEG2 that were not previously known to be expressed by these cells.

IM6

THE SHP-1 MODULATION OF CD19 TYROSINE PHOSPHORYLATION IS MEDIATED THROUGH DEPHOSPHORYLATION/DEACTIVATION OF THE LYN PROTEIN TYROSINE KINASE. Ally-Khan Somani*, Fenhao Xu, Jinyi Zhang, Xuwen Song and Katherine A. Siminovitch. Departments of Immunology, Medicine and Molecular and Medical Genetics, University of Toronto, The Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Ontario, M4Y 1J3, Canada

SHP-1 is a cytosolic tyrosine phosphatase implicated in the downregulation of signaling cascades coupling the B cell antigen receptor (BCR) to cell proliferation. SHP-1 effects on BCR signaling appear to reflect its capacity to interact with and dephosphorylate several BCR comodulators including CD22 and FcγRIIB1. In view of our observation that CD19 tyrosine phosphorylation is constitutively increased in B cells from SHP-1-deficient motheaten mice, we investigated the possibility that CD19 represents another BCR comodulator susceptible to SHP-1 dephosphorylation. However analysis of CD19 coimmunoprecipitable tyrosine phosphatase activity in CD19 immunoprecipitates from both motheaten and wild-type B cells and from SHP-1 immunodepleted wild-type cells revealed that SHP-1 accounts for only a minor portion of CD19 associated tyrosine phosphatase activity. In contrast, CD19-associated Lyn tyrosine kinase activity from both resting and BCR-induced B cells was found to be markedly increased in *me*^{v} compared to wild-type. In view of the important role for Lyn kinase in the phosphorylation of CD19, we investigated the influence of SHP-1 on Lyn. Herein we show that both constitutive and BCR-induced Lyn tyrosine kinase activity to be also markedly increased in *me*^{v} compared to wild-type B cells. The data also revealed association of SHP-1 with Lyn in BCR stimulated WEHI-231 cells and the capacity of Lyn to interact with the SHP-1 NH2-terminal SH_2 domain *in vitro*. These data, together with cyanogen bromide cleavage data revealing the capacity of SHP-1 to dephosphorylate the Lyn autophosphorylation site (Y397), provide strong evidence that SHP-1 functions include the negative regulation of Lyn activation in B cells. Thus Lyn deactivation/dephosphorylation represents a likely mechanism whereby SHP-1 exerts its influence on CD19 tyrosine phosphorylation and, by extension, its inhibitory effect on BCR signaling.

IM7

THE SHP-1 TYROSINE PHOSPHATASE INHIBITS ANTIGEN RECEPTOR INDUCED APOPTOSIS OF ACTIVATED PERIPHERAL T CELLS. Ally-Khan Somani*, Jinyi Zhang and Katherine A. Siminovitch. Departments of Immunology, Medicine and Molecular and Medical Genetics, University of Toronto, The Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Ontario, M4Y 1J3, Canada

Restimulation of antigen receptors on peripheral T lymphocytes induces tyrosine phosphorylation-based signaling cascades which evoke Fas ligand expression and induction of Fas-mediated programmed cell death. In view of the role for the SHP-1 tyrosine phosphatase in modulating TCR signaling, we investigated the influence of SHP-1 on TCR-mediated apoptosis by assaying the sensitivity of peripheral T cells from SHP-1 deficient viable motheaten (mev) mice to cell death following TCR restimulation. The results of these studies revealed mev peripheral T cells to be markedly more sensitive than wild-type cells to induction of cell death following TCR stimulation. By contrast, PMA/ionophore and anti-Fas antibody induced apoptotic responses were no different in mev compared to wild-type activated cells. Enhanced apoptosis of TCR-restimulated mev lymphocytes was associated with marked increased Fas ligand expression as compared to wild-type cells, but was almost abrogated in both mev and wild-type cells by Fas-Fc treatment. Thus, the increased sensitivity of mev T cell to apoptosis following TCR restimulation appears to reflect a TCR-driven phenomenon mediated through upregulation of Fas ligand-Fas interaction and induction of the Fas signaling cascade. These findings, together with the hyperproliferative responses of mev peripheral T cells to initial TCR stimulation, indicate that SHP-1 modulation of TCR signaling translates to the inhibition of both T cell proliferation and activation and as such is likely to play a pivotal role in regulating the expansion of antigen-stimulated T cells during an immune response.

Infectious Disease and Microbiology

ID1

STRUCTURE-FUNCTION STUDIES OF A VIRAL RNA-DEPENDENT RNA POLYMERASE (RDRP). R. Goswami*, K. M. Coombs. Dept. of Medical Microbiology, University of Manitoba, Winnipeg, Manitoba, Canada, R3E 0W3.

Gastroenteritis is the greatest cause of death, worldwide. It has been estimated that 5-10 million Third World children die each year from diarrheal diseases, rotavirus infections in malnourished children being a major contributor. Reovirus and rotavirus are both members of the family *Reoviridae* and use similar RDRP enzymes to replicate their respective genomes. In this study, a temperature sensitive reovirus mutant was examined to gain insight into the characteristics of the RDRP. The temperature sensitive mutant under study (*ts585*), possesses a point mutation through treatment of reovirus T3D with nitrosoguanidine (Fields and Joklik, 1969; Ito and Joklik, 1972). This mutation is hypothesized to be within the reoviral L1 gene segment which encodes for the protein λ3, the RDRP. The overall goals of this study are to confirm that the reoviral clone 585 is indeed temperature sensitive, that the temperature sensitive lesion is within the L1 gene segment, and that the lesion affects the production of both ss and dsRNA through a change in primary structure of the protein, λ3. The main objectives of the project that were to be completed this year were to confirm the temperature sensitive nature of reovirus clone 585, and to map the temperature sensitive lesion to a specific gene segment if temperature sensitivity is confirmed. We have demonstrated temperature sensitivity in clone 585. Temperature sensitivity in reovirus is demonstrated as impaired replication in mouse L929 cells expressed as an efficiency of plating (EOP) value. Wild-type virus will exhibit an EOP of 0.1-1.0 whereas a temperature sensitive clone will have an EOP at least one order of magnitude below wild-type (ie. EOP≤0.01). In this study, clone 585 exhibited EOP's ranging from 10^{-5} to 10^{-6}, clearly demonstrating that it is indeed temperature sensitive. Reassortment mapping was carried out to map the temperature sensitive lesion to a particular reoviral gene segment. Once the lesion is properly mapped, the functional significance of the lesion must be determined. Sequencing of the mutated gene segment and comparison of the obtained sequence to the wild-type sequence will then be carried out to determine any primary structure changes in the mutated segment. A thorough characterization of the temperature sensitive lesion in *ts585* will be continued in the near future.

ID2

THE MORBIDITY & MORTALITY OF PEDIATRIC SPLENECTOMY: DOES PROPHYLAXIS MAKE A DIFFERENCE? Martin Jugenburg*, Graham Haddock, Melvin H. Freedman, Lee Ford-Jones, Sigmund H. Ein,
Divisions of General Surgery, Hematology, and Infectious Diseases; The Hospital for Sick Children, University of Toronto, Canada, M5G 1X8

Purpose: To analyze the incidence of post-splenectomy sepsis morbidity and mortality after prophylaxis, in comparison to our previous 13-year study (1958-1970 inclusive).
Methods: All patients who had splenectomy at the Hospital for Sick Children, Toronto, between 1971 and 1995 inclusive (to give a minimum of two years for follow-up) were reviewed for infection and mortality. The criterion for classifying a patient as "infected" was the recovery of an invading encapsulated organism from the blood culture in a patient admitted to the hospital.
Results: Of the 264 patients studied, 10 had a post-splenectomy infection (3.8%); nine occurred in patients splenectomized between the ages of 0-5 years. Infection took place within 2.13 years ± 3.25 (mean ± SD) after splenectomy for the vaccinated patients and 11 days ± 5 (mean ± SD) for the non-vaccinated children. A significant number of patients had admission due to an apparent respiratory infection, but no serum organisms were isolated. One died of overwhelming sepsis, but the responsible organism was not identified.
Conclusion: Although there has not been a decrease in the number of splenectomies performed per year, the incidence of infection and mortality has decreased by 47% and 88% respectively with prophylaxis.

ID3

IN VITRO EVIDENCE IN SUPPORT OF AN OUTBREAK DUE TO CONJUGATIVE TRANSFER OF *VANA* GENES INTO A HOSPITAL'S ENDEMIC VANCOMYCIN-SUSCEPTIBLE ENTEROCOCCI. M.M. KAPALA*, B.M. WILLEY, F. ARCE, G. LARGE, A. MCGEER, D.E. LOW. Dept. of Microbiology, Mount Sinai Hospital; Dept. of Medicine, University of Toronto; and Scarborough General Hospital.

In Jan 1997, during a vancomycin-resistant enterococcal (VRE) outbreak in a community hospital, evidence was found of *vanA* transfer from the index VR-*E. faecium* to three unrelated Vancomycin-Susceptible Enterococci (VSE) endemic to the hospital. Clonal relatedness of the VRE and VSE was discovered during molecular characterization of outbreak isolates using *Sma*I PFGE. Transmission of the index VRE did not occur, but 28 patients became colonized with 1 of 3 VSE clones which had acquired *vanA* from the index VRE. *In vitro* filter mating experiments were performed to determine the *vanA* transfer rate from the index VR-*E. faecium* to 2 VS-*E. faecium* and the VS-*E. faecalis* endemic to the outbreak hospital. We compared these rates to those of a *vanA*-containing VR-*E. faecium* associated with monoclonal VRE epidemics. The *vanA* transfer rates from the index VR-*E. faecium* to the 2 VS-*E. faecium* and the VS-*E. faecalis* were $1.1x10^{-5}$, $6.9x10^{-6}$ and $2.6xI0^{-7}$, respectively. By comparison, rates of transfer from the epidemic VR-*E. faecium* were $4.2x10^{-6}$, 0 and 0 to the same 3 VSE. Probing found the *vanA* gene to reside on a ~50-60Kb fragment that did not insert into pre-existing chromosomal bands. The high transfer rate from the index VRE to the endemic VSE provides a laboratory model of what occurred in the hospital setting leading to the VRE outbreak. Results suggest the *vanA* transposon is resident on a large, highly promiscuous, conjugative plasmid, and rapid VRE spread in this setting resulted from high frequency transfer of this plasmid from the index VRE to multiple endemic VREs well adapted to transmission and survival within the hospital environment. As some investigators have shown that Long-PCR identifies variability in the *vanA* gene cluster, Tn1546 primers were used to amplify a ~10.4Kb fragment of the cluster from the index and one endemic clone. The amplicons were restricted using *ALW* I and RFLP patterns compared. As variability among various clones of VRE has been demonstrated by this method, the identical patterns that were seen indicate a close relatedness between the two clusters. However, the epidemic clone used as a comparator strain in the mating experiments proved to be highly similar, suggesting a relatedness between the different clones. Such evidence may help to explain the speed of spread of VRE and the frequent occurrence of multi-clonal outbreaks.

International Health

IH1

THE FELT HEALTH NEEDS OF NAIROBI STREET CHILDREN, PAST AND PRESENT. J.S. Tibbet*, C. Chalin, T. Olewe. International Health Program, Faculty of Medicine, University of Toronto.

Recent rises in Kenyan urban populations due to rapid political, social and economic changes have expanded urban poverty. With concomitant increases in school dropout rates and the rising incidence of AIDS, youth are being forced into the streets. Despite the efforts of non-governmental organizations, churches and the government, the number of street children continues to grow. Myths about street culture act as barriers to health care and this calls for direct insight into the experiences of these children.

This study was conducted to gain preliminary knowledge on the perceived health needs Nairobi street children. In conjunction with future research, it is intended to contribute to efforts of the Presbyterian Church of East Africa (PCEA) in setting up health services for this population.

Two survey instruments were designed following consultation with key informants onsite and were administered with the assistance of Kiswahili translators. The four components of an interview were administered to a small sample of boys and this was followed by a questionnaire on health-related perceptions, which was given to a larger group (n=54). Participants included current street boys as well as those who are in rehabilitation homes, providing insight into the views of past street children as well as the perspectives of current street dwellers.

Data were analyzed qualitatively and emergent themes included basic needs (food, shelter, water and school), health care access, immunization, abuse, exercise, awareness, drugs, sexual behaviour and reasons for coming to the street. Recommendations were made to the PCEA to assist in guiding future health initiatives.

IH2

ATTITUDES TOWARDS THE TREATMENT AND CARE OF PERSONS WITH AIDS IN JIMMA, ETHIOPIA. T.R. Harris*, S.B. Wilton*, D. Zakus, H. Argaw. International Health Program, Faculty of Medicine, University of Toronto, Canada, M5S 1A8. Department of Community Health, Jimma Institute of Health Sciences, Jimma, Ethiopia.

The prevalence of AIDS is increasing exponentially in Ethiopia. Due to a lack of access to health care or effective anti-viral medications, persons with AIDS (PWAs) in Ethiopia often receive only rudimentary community care. Very little is known about the attitudes community members have towards these people and their care. We hypothesized that increased personal contact with PWAs and increased factual AIDS knowledge would be correlated with more empathic attitudes. To investigate this, we designed a survey that included questions regarding basic knowledge of AIDS, as well as attitudes towards the treatment and care of PWAs. These questions were scored, so that knowledge and attitude levels could be compared with various demographic factors. We trained eight Ethiopian health care workers to administer the survey to randomly selected individuals from three distinct populations. A total of 1142 health clinic attendees, health care providers, and Jimma Institute of Health Sciences (JIHS) students were interviewed over a one week period in July, 1998. Preliminary results support our hypothesis, and a full statistical analysis is forthcoming. Our conclusions will indicate which Ethiopian sub-populations can most benefit from future AIDS education initiatives. More empathic attitudes should translate into better community care and improved quality of life for PWAs in Ethiopia.

IH3

CAREGIVER ATTITUDES TOWARDS HIV TESTING IN CHILDREN IN BLANTYRE, MALAWI.

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Blantyre, Malawi is estimated to have an adult HIV infection rate of over 25%. The precise infection rate in children is not known but it is estimated to be similar to adult rates. Staff at the Queen Elizabeth Central Hospital, Blanytre, are faced on a daily basis with children who they suspect to be infected with HIV. With all of the sensitive cultural issues associated with HIV infection in Malawi and the fact that no treatment is available, they struggle with the issue of whether or not to test these children. The purpose of this study was to gain an understanding of the attitudes towards HIV testing in children held by their caregivers. The goal was to provide health care providers in Blantyre with guidance for raising the issue of testing with caregivers.

One hundred and five surveys were completed by caregivers of children in the paediatric wards and clinics of Queen Elizabeth Central Hospital. The caregivers where selected based on their child's illness. The children connected to the study were either being investigated or treated for tuberculosis or HIV/AIDS. All surveys were completed using a structured interview conducted in Chichewa. Hospital staff and students acted as translators.

Overall attitudes towards testing were positive with 83% of respondents feeling that it was good for parents to know their child's HIV status and 98% feeling that it was good for doctors to know a child's status. 75% felt that all children admitted to hospital should be tested. However, several misconceptions about the hospital's policies and practices with respect to HIV testing were revealed. 27% indicated their belief that all children admitted to hospital are tested. 29% felt that they did not have the right to refuse testing for their child.

Therefore, the staff at Queen Elizabeth Central Hospital can feel comfortable raising the issue of testing with caregivers since a majority appear to be open to the idea However, they also need to be vigilant to clarify misconceptions about the hospital's testing policies.

Medical Education

ME1

MEDICAL TRAINEES' ATTITUDES TOWARDS MULTICULTURAL HEALTH EDUCATION IN UNDERGRADUATE AND POSTGRADUATE PROGRAMS

Kohn ML, Regehr G, Keystone JS

Faculty of Medicine, International Health Program, University of Toronto

Despite Canada's increasingly diverse population, there has been little focus on multicultural issues in Canadian medical programs. Although some schools have attempted to implement a multicultural curriculum, the exact content and the trainee's impressions of its success have not yet been thoroughly investigated. To assess the perceived quality of multicultural health education in Ontario, a survey was distributed to 515 residents within Medicine, Surgery and Family Medicine programs across the province.

Of the 515 questionnaires mailed out, 262 (51%) were completed and returned. The need for multicultural health training was clear. Sixty-seven percent of respondents indicated that they cared for a culturally diverse population, with 44% reporting that greater than 25% of their population was culturally diverse. Ninety-one percent reported a need for multicultural health programs in undergraduate programs and 83% responded accordingly for postgraduate programs. Ninety-four percent of the residents trained in an Ontario medical school reported receiving some form of multicultural education. Of those individuals, 13% had a formal, mandatory course, 41% participated in electives, 61% were offered extra seminars or workshops and 18% received multicultural training in some other unspecified form. Fifty-six percent believed that there was some effort to integrate the topic into the curriculum.

However, in evaluating the adequacy of their undergraduate programs' efforts in multicultural training, 48% indicated that the quality of training was poor and only 11% considered it to be excellent. Consistent with these results, residents rated their comfort level in caring for individuals from diverse cultural backgrounds at an average of 3.6 on a scale from 1 (very uncomfortable) to 5 (very comfortable). Only 55% indicated a comfort level as high as 4 or 5.

These results suggest that medical trainees perceive a definite need for multicultural health education in undergraduate and postgraduate training programs. Despite some efforts in this direction by Ontario medical programs, the needs of the trainees are not being adequately fulfilled at this time.

ME2

ATTITUDES, LEVEL OF COMPETENCE, AND FEAR OF MEDICAL STUDENTS AND RESIDENTS TOWARD CARE OF DYING PATIENTS.

R. Fung*, F.D. Ferris. Temmy Latner Centre for Palliative Care, Mount Sinai Hospital, University of Toronto, Canada, M5G 1X5.

We believe that attitudes, fear and lack of knowledge about care for dying people set during undergraduate and postgraduate medical education lead to major barriers to good palliative care. To test our hypothesis, we set out to assess the prevailing attitudes, fears and level of competence of medical students and residents about care of the dying and to identify aspects of medical education which could give rise to such attributes.

With a view to developing a survey for wide administration, we reviewed the literature and conducted focussed interviews with 5 palliative care physicians, 5 physicians in other specialties, 4 other health care professionals, 4 residents, 5 medical students, and 4 patients. Qualitative techniques were used to encode the interview data and extract the major themes.

Already, our interviews have shown that end of life care receives low priority in medical education. There is no systematic way in which medical students are ensured of having any clinical experience caring for dying people, though most interviewees agreed that "seeing good palliative care in action" is the best way to learn it. Even when they do have experience, these are extremely variable. In the setting of acute care medical/surgical wards, there is a definite focus on acute medical problems with palliative care issues receiving little or no attention, depending on the supervisor. The lack of knowledge in palliative medicine and the low priority that it receives in the minds of physicians are perpetuated from physician to student down the generations. This phenomenon is supported by many studies which show the poor quality of end of life care and the lack of competency of medical students and residents towards management of pain and end of life decision-making. Frequently, prevailing attitudes were shown to be detrimental to good clinical care for seriously ill patients. Recognition of the importance of palliative care and its integration into mainstream medicine and medical education are essential steps if we are to provide quality care to our dying.

ME3

EXAMINATION OF THE U of T UNDERGRADUATE MEDICAL SCHOOLCURRICULUM AND STUDENTS' COMPETENCE IN ADDRESSING ISSUES OF WOMAN ABUSE. T. Shainhouse*. University of Toronto, Canada, M5S 1A8

Abuse against women is now well recognized as a social problem that has serious health consequences, both physical and psychological. Graduate and student physicians are in an important position to recognize and expose the abuse against their patients, and counsel and advocate for women as the need arises. Unfortunately, many unskilled physicians still believe violence is a private matter with which they should not tamper; or else, they feel helpless in trying to approach and address the complexity of the problem. More problematic, however, is that much of the somatization of abuse is not being recognized as such. This project involved theme-mapping of the U of T undergraduate medical curriculum, as well as surveying the U of T medical student body, to explore whether or not issues surrounding woman abuse are being adequately and effectively addressed at the undergraduate medical education level. The outcomes of the investigation indicate that most students have not learned how to screen for woman abuse, nor do they routinely screen for abuse (68.4% and 95%, respectively). Furthermore, 77.4% of students responded that they would like to see more information on responding to the health needs of abused women included in the undergraduate medical curriculum. These results suggest that this undergraduate curriculum needs improvement, so as to produce physicians who are interested and skilled in recognizing the effects that assault has on the presentation of disease, and in detecting and dealing with potentially abused women.

Medical Genetics

MG1

ASSOCIATION OF GENETIC MARKERS FOR THE SODIUM-HYDROGEN ANTIPORTER TYPE 3 (NHE3) WITH ESSENTIAL HYPERTENSION IN ICELANDIC PEDIGREES. Brian H. Buck[1], A.D.Paterson[2], J.L. Kennedy[2], G. Thorgeirsson[3], S, Sigurdsson[4], D.M.J. Naimark[1]. Sunnybrook & Women's College Hospital[1] & The Clarke Institute[2] University of Toronto, Canada M4N 3M5, The National University Hospital[3] & the Department of Physiology, University of Iceland, Reykjavik, Iceland, IS-101[4].

Introduction Evidence from animal models and human renal transplantation suggests that the kidneys are involved in the pathogenesis of essential hypertension. The shift of the pressure-natriuresis curve to the right in hypertensives implies that a defect in sodium handling exists. Most Na+ reabsorption occurs in the proximal tubule via the apical NHE3 which has been mapped to 5p15.3. The Icelandic population is especially suited for the detection of hypertension genes because of a high degree of genetic homogeneity plus their program of population-wide cardiovascular risk factor screening. **Hypothesis** The 5p15.3 region contains a susceptibility locus for essential hypertension in Icelandic pedigrees. **Methods** The Icelandic Heart Association screens individuals in Reykjavik for cardiac risk factors. Hypertensive individuals are referred to a specialized clinic. Records from this clinic were reviewed and probands with a family history of hypertension were identified. 20-30ml of venous blood was collected from the probands and all available family members. DNA was extracted from the peripheral leukocytes by a non-enzymatic method [Lahiri, 1991]. Genotyping assays are being conducted. Two markers in the NHE3 region, D5S1981 and D5S2005 are being amplified via PCR using primers obtained from Research Genetics Inc. (Philadelphia, PA) The genetic data will be analyzed by comparing the number of marker alleles identical-by-descent (ibd) in concordant-affected versus discordant and concordant unaffected sib-pairs via $\chi 2$ analysis. **Results** Four pedigrees were obtained with 35 individuals available for blood sampling. 12 of 35 individuals had hypertension (bp>140/90 on 3 clinic visits ± 24hrABP monitoring + on treatment) while 23 are currently unaffected. ~ 200 µg of DNA has been obtained from each subject. Genotyping is nearly completed. **Discussion** This is a preliminary analysis, further pedigree ascertainment & genotype analysis will be required to determine whether the NHE3 locus is associated with human essential hypertension.

Medical Imaging

MI1

DEVELOPMENT OF A NEW MRI SCANNING PROTOCOL FOR THE BRAIN E.R.J.Sacttler*, M.L Wood. Sunnybrook Health Science Centre, Imaging Research, Room S654, 2075 Bayview Ave. North York, Ontario, Canada, M4N 3M5

MRI images depict cross-sectional slices of anatomy. In conventional MRI, slices of uniform thickness are acquired over the entire scanned area. Thin slices reduce the chance of missing a small lesion, but the images are noisier and it takes more slices and correspondingly more time to cover a given region of anatomy. A new technique, recently developed by Dr. Michael Wood's group at Sunnybrook Health Sciences Centre, allows thinner slices to be obtained in areas where abnormalities are more probable, while thicker slices are obtained over a larger area for security of complete coverage. The technique, known as *wavelet encoding*, is innovative in the way in which thin and thick slices are combined in a pyramid-like arrangement. Not only can this technique provide thinner slices than conventional methods, but if the thin slices prove to be unacceptably noisy, they may be retroactively *thickened*, and will be of higher quality than conventionally obtained thick slices. Another related imaging technique known as *Hadamard encoding* produces a set of slices of uniform thickness similar to conventional techniques, but with better signal-to-noise ratio and correspondingly better image quality in equal or less time. Following a period of technical development, a preliminary clinical evaluation of the two methods was carried out. For this evaluation we chose scans which covered the region of the pituitary with sagital and coronal slices, and scans which covered the internal auditory canals (IAC's) with axial slices. For comparison, control images were obtained at the same time using a conventional scanning technique. Normal volunteers were used for the pituitary scans. Scans of the IAC's were obtained on a patient with known pathology (acoustic neuroma). The images were be evaluated for their diagnostic quality, specifically their sharpness, and for the absence of unwanted structures (artifacts) and noise. Quantitative measurement of the signal-to-noise ratio was in good agreement with the theoretical value, indicating that a significant gain in image quality may be obtained with the new techniques. Future work on this project will involve an evaluation of the wavelet encoding technique on a specific high-volume protocol, either involving the pituitary or the IAC's. Ultimately this technique should improve the quality of MR images in a wide variety of protocols.

MB1

INVESTIGATING THE FUNCTIONAL INVOLVEMENT OF VAMP2 AND VAMP3/CELLUBREVIN IN THE INSULIN-STIMULATED TRANSLOCATION OF GLUT4 TO THE PLASMA MEMBRANE OF L6 MUSCLE CELLS. N.Daneman*, P.Bilan, A. Klip. Division of Cell Biology, the Hospital for Sick Children, University of Toronto, Canada, M5G 1X8.

In peripheral muscle and adipose tissue, insulin stimulates the translocation of glucose transporters (GLUT4) to the plasma membrane. This process is believed to involve non-neuronal homologues of the SNARE proteins required for synaptic vesicle docking and fusion in neurons. Previous studies have characterized the muscle cell's v-SNAREs (VAMP2 and VAMP3/cellubrevin) and t-SNAREs (SNAP-23 and syntaxin4). In this study, we attempt the first demonstration of a functional involvement of VAMP2 and/or VAMP3 in the translocation of GLUT4 to the plasma membrane of muscle cells, as well as the first determination of the relative importance of these two proteins in peripheral insulin action. To this end we cultured L6 muscle cells expressing a recombinant GLUT4-myc fusion protein These cells were transiently transfected with various combinations of constructs, including: enhanced green fluorescence protein (EGFP), tetanus toxin light chain (Ttx-LC), and tetanus-resistant VAMP2 and VAMP3 mutants. A portion of these cells were stimulated with insulin, and then all cells were subjected to immunofluorescence. EGFP signal was used to locate transfected cells, while surface immunofluorescent staining of the myc epitope was used to assess GLUT4 translocation to the plasma membrane. Under optimal conditions, EGFP visualization indicated that transfection efficiency exceeded 50%. As hypothesized, insulin stimulation led to an increase in surface GLUT4-myc staining, and this increase was abated by Ttx-LC which is known to cleave both VAMP2 and VAMP3 proteins. GLUT4 translocation was rescued by cotransfection with a tetanus-resistant mutant of VAMP2, but not by cotransfection with the corresponding VAMP3 mutant. Hence, our study has implicated VAMP2, and not VAMP3, in the insulin-stimulated translocation of GLUT4 vesicles to the plasma membrane of L6 muscle cells.

MB2

ANDROGEN INDUCTION OF NF-κB IS IMPORTANT FOR PROSTATE TUMOUR CELL SURVIVAL. Richard Bitar*, R. William G. Watson, Ronan Coffey, John Fitzpatrick. Department of Surgery, Mater Misericordiae Hospital, University College Dublin, Dublin 7, Ireland.

The adult male prostate depends continuously upon a supply of androgen to maintain an equilibrium between cell proliferation and death. Androgen ablation induces apoptosis in prostate glandular epithelial cells. Androgen inhibition of apoptosis may be mediated through the production of survival factors. The NF-κB family of transcription factors have been associated with resistance to apoptosis. We hypothesized that NF-κB is a central transcription factor required for the survival of androgen dependent prostate cells. LNCaP cells were cultured with and without 5-α-Dihydrotestosterone (5-α-DHT, 10^{-8}M) and assessed for their susceptibility to etoposide (VP-16)-induced apoptosis by PI DNA staining. 5-α-DHT treated cells were resistant to etoposide induced apoptosis (Table)

Table	% apoptosis
LNCaP	7.98 ± 2.91
LNCaP + 5-α-DHT	14.60 ± 4.95
LNCaP + VP-16 120μM	16.80 ± 3.68*
LNCaP + 5-α-DHT + VP-16 120μM	15.98± 3.47**
LNCaP + PDTC 10μM	5.1 ± 1.12†
LNCaP + 5-α-DHT + PDTC 10μM	33 ± 15.89§

Results: mean±SD, * $p<0.05$ vs. LNCaP, ** NS vs. LNCaP + 5-α-DHT, † NS vs. LNCaP, § $p<0.05$ vs. LNCaP + 5-α-DHT. Statistical analysis by ANOVA. n=5 for all groups.

5-α-DHT increased NF-κB binding activity as assessed by EMSA. An increase in Bcl-X_L protein expression, an important survival factor, was also observed. To further confirm the role of NF-κB in 5-α-DHT induced survival of LNCaP cells, PDTC (a NF-κB inhibitor) was incubated with LNCaP cells treated with or without 5-α-DHT. PDTC significantly induced apoptosis only in the 5-α-DHT treated cells in a dose dependent manner, but had no effect on control LNCaP cells (Table). In conclusion, 5-α-DHT induces NF-κB binding activity and the expression of Bcl-X_L in LNCaP cells. This induction not only generates resistance to etoposide-induced apoptosis, but is also central to the survival of androgen-treated LNCaP cells. This study demonstrates for the first time the role of NF-κB in androgen-treated LNCaP cells, and may represent a novel target for future therapeutic strategies.

MB3

RGS4, A SIGNALING LINK BETWEEN G PROTEINS AND MAPK IN PC12 CELLS. **Aleixo Muise* & Harry Elsholtz. Department of Laboratory Medicine and Pathobiology, Faculty of Medicine, University of Toronto, 100 College St., Toronto, Canada, M5G 1L5**

Many fundamental biological processes are controlled by cell signaling. There is growing evidence that several disease states, including endocrinopathies and cancer, are caused by activating mutations in G protein coupled receptors and trimeric G proteins, as well as by alterations in tyrosine kinase receptors and their associated signaling molecules including MAP Kinase. A recently identified protein family named regulator of G protein signaling (RGS) has been shown to act as a negative regulator of G proteins through stimulation of hydrolysis of GTP bound to the activated Gα. RGS4 has also been implicated in the regulation of MAPK activation. In these studies, the role of RGS4 (an RGS protein expressed primarily in brain, heart, and cell lines of adrenal and pituitary origin) in G protein and MAPK signaling is explored.

Using neuronal phaeochromocytoma PC12 cells, immunoprecipitation studies and subsequent Western blot analysis showed that two forms of RGS4 exist. To determine if the two forms corresponded to a phosphorylated and dephosphorylated form, in vitro kinase assays were carried out. These studies showed a novel post-translational modification of recombinant purified RGS4 through phosphorylation. Further studies showed that RGS4, but not another RGS protein GAIP, was phosphorylated by a variety of MAPKs. To determine which MAPK was responsible for phosphorylation of RGS4 in PC12 cells, in-gel kinase assays were performed. These results demonstrated that the MAPKs ERK1/2 were the specific kinases responsible for RGS4 phosphorylation. Interestingly, ERK2 was also found to co-immunoprecipitate with an antibody directed towards RGS4, and likewise the dephosphorylated form of RGS4 co-immunoprecipitated with an antibody directed towards ERK2 in PC12 cells.

The results show that RGS4 and MAPK interact either directly or indirectly in a complex that may control the atypical G protein regulation of MAPK in PC12 cells. Further investigation into the mechanism by which MAPK phosphorylation of RGS4 regulates its inhibitory effect on Gα, and the role that RGS4 plays in linking G protein and MAPK signaling are underway. These studies may help to elucidate the signaling cascades necessary for neuronal differentiation, and give greater insight into the mechanisms of control of these key signaling molecules.

MB4

CHARACTERIZATION OF THE *Drosophila melanogaster* HOMOLOGUE OF NEDD4. P.C. Henry*, D. Rotin. Cell Biology, Hospital for Sick Children, University of Toronto, Canada, M5G 1X8.

Nedd4 is a ubiquitin-ligase protein which was identified as a binding partner for the proline-rich (PY motif) C-terminus of the β-subunit of the epithelial sodium channel (ENaC) by yeast two-hybrid library screening. A *Drosophila* homologue of Nedd4 (dNedd4) contains a C2 domain, 3 WW domains (to which the PY motif binds) and a C-terminal Hect domain, a domain with catalytic activity involved in the targeted degradation of other cellular proteins by proteasomal or lysosomal systems. Nedd4 has the potential to participate enzymatically in many cellular pathways via its multiple WW protein-interaction domains. Thus its biological role in the cell is being studied in *Drosophila*, a biological system that can be easily manipulated genetically.

dNedd4 cDNA was cloned by screening a *Drosophila* embryo expression library with the PY motif of Inscuteable, a *Drosophila* protein, as bait. dNedd4 has been localized by chromosome *in situ* hybridization to the left arm of the 3rd chromosome in the genome. Precise genomic mapping of subcloned genomic DNA containing dNedd4 cDNA sequence will facilitate the generation of dNedd4 mutant strains for biochemical and biological characterization.

The GAL4 driver/UAS promoter system is being used to create transgenic *Drosophila* strains which over-express wild-type and ubiquitin-ligase dominant-negative versions of dNedd4 during different stages of development and in various tissue distribution patterns. Characterization of these strains is in progress.

Neuroscience

NS1

THE EFFECT OF EARLY MONOCULAR DEPRIVATION ON THE DISTRIBUTION OF NMDAR1 SUBUNIT IN VISUAL CORTEX. Victor D. Pegado, Kevin R. Duffy, Christopher Trepel & Kathryn Murphy. Departments of Psychology and Biomedical Sciences, McMaster University, Hamilton, L8S 4K1.

Monocular deprivation during the critical period in early postnatal development, causes physiological, anatomical, and behavioural changes. This plasticity in the kitten visual cortex is mediated by the activation of the NMDA receptor. Although previous studies report high levels of the NMDA receptor in area 17 during the critical period, long-term visual recovery from early monocular deprivation is very limited even when terminated during this period. To further examine this issue we have studied the distribution of NMDAR1immunoreactive(ir) neurons in section from unfolded and flattened visual cortex of either normally reared or monocularly deprived kittens (3 - 6 weeks of age). NMDAR1ir neurons were plotted from different regions of area 17 representing central or peripheral visual field. There was an obvious loss of NDAR1ir neurons in the supragranular layers within the region of area 17 where the central visual field is represented. Thus the effect of monocular deprivation is not uniform across the extent of area 17. These results suggest that the reçovery of vision following early monocular deprivation may be limited by a loss of the NMDA receptor in the central visual field representation.

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Obstetrics and Gynecology

OB1

THE GYNECOLOGICAL FINDINGS OF GRAFT-VERSUS-HOST-DISEASE: EXAMINING THE CORRELATES. A. Hosokawa*, C. Derzko, H. Messner, W. Chapman, T. Panzarella. Department of Obstetrics and Gynecology, St. Michael's Hospital; Ontario Cancer Institute, Princess Margaret Hospital, Toronto, Canada, M5C 2T2/M5G 2M9.

Chronic graft-versus-host disease (GVHD) is a systemic, multi-organ syndrome that can develop in patients several months after a bone marrow transplant (BMT). Although there is little evidence in the literature citing the gynecological manifestations of GVHD, clinical evidence shows that post-BMT patients can develop vaginal inflammation, sicca syndrome, adhesions, and stenosis – symptoms which are thought to be associated with the disease process. Therefore, *the objective of this study has been to examine the factors which are associated with vaginal GVHD in post-BMT patients and to develop a descriptive profile of these patients, including the clinical manifestations and histological findings.* It has been hypothesized that increasing recipient age, human leukocyte antigen (HLA) disparity, severity of prior acute GVHD, and greater number of target organ involvement will increase the likelihood of developing the gynecololgical manifestations since these are all factors which are associated with the development of chronic GVHD, in general. The study involved the examination of medical records and vaginal biopsy slides of 32 female post-BMT patients of Princess Margaret Hospital, of which 13 were suspected of having GVHD of the vagina. Results from this study indicate that there is a positive correlation between the proportion of individuals with vaginal GVHD and the total number of organ systems involved in the disease other than the vagina. There was no significant relationship between the occurrence of vaginal GVHD and the other factors that were examined. The clinical characteristics involve vaginal dryness, stenosis, inflammation, and erythema with secondary dyspareunia, reduced libido, and hematometra/hematocolpos. The histological findings obtained through vaginal biopsies showed epithelial desquamation, fibrosis, and inflammation with a nonspecific infiltration of polymorphs in 62% of cases. Given the preceding evidence, it is postulated that these gynecological manifestations are a sequelae of chronic GVHD or indirectly associated with the disease process. However, there are more likely several different mechanisms at play to account for the gynecological abnormalities seen in post-BMT patients, which can hopefully be elucidated with further studies in this area.

OB2

EFFECT OF PRENATAL GLUCOCORTICOID EXPOSURE ON PITUITARY PRO-OPIOMELANOCORTIN AND GLUCOCORTICOID RECEPTOR EXPRESSION IN JUVENILE GUINEA PIGS

Catherine L. Yu*, Farrah Dean and Stephen G. Matthews, Department of Physiology and Department of Obstetrics and Gynecology, Faculty of Medicine, University of Toronto, Canada M5S 1A8

In North America, approximately 10% of pregnant women receive synthetic glucocorticoids (GC) to promote fetal lung development, when risk of pre-term delivery is identified. However, recent studies indicate that prenatal exposure to GCs alters the development of the hypothalamic-pituitary-adrenal axis and its subsequent function after birth. In the present study, we hypothesized that such alterations in HPA function are associated with changes in the expression of pituitary glucocorticoid receptors (GR) and pro-opiomelanocortin (POMC) mRNA.

Fetal guinea pigs were prenatally exposed to dexamethasone (1 mg/kg DEX - a GC analogue) or vehicle (control) on day 50 and 51 of gestation. At 18 days of age, the juvenile guinea pigs were killed and the pituitaries removed and cryosectioned. Analysis of POMC mRNA in the intermediate and anterior lobes of the pituitary, and GR mRNA in the anterior lobe of the pituitary was undertaken using *in situ* hybridization.

DEX-treated animals demonstrated lower levels of POMC mRNA in the intermediate lobe compared to vehicle-treated animals. No significant differences between DEX-treated and vehicle-treated animals were found for POMC mRNA or GR mRNA levels in the anterior lobe. However, a significant sex difference was found for POMC mRNA levels in the anterior lobe of the pituitary; females showed higher levels of POMC mRNA in the anterior lobe compared to males. In conclusion, prenatal exposure to glucocorticoid has long term effects on function of the intermediate pituitary. We speculate that this results from GC-induced changes in development of central dopaminergic control.

OB3

WOMEN'S PREFERENCES FOR TREATMENT FOLLOWING A MISSED ABORTION. A. B. Montgomery*, S. Dunn. Bay Centre for Birth Control, Women's College Hospital, 790 Bay St., University of Toronto, Toronto, ON, Canada, M5G 1N9.

The three methods for treating missed abortions that occur early in the first trimester are surgical evacuation of the pregnancy products (dilatation & curettage), medical evacuation (administration of misoprostol), and expectant management. The latter two methods have the advantage of avoiding surgery, while a D&C provides prompter resolution of the miscarriage. Previous studies have indicated women's dissatisfaction with miscarriage management. We were interested in women's treatment preferences and follow-up requirements following a miscarriage. We asked women who had experienced a miscarriage in the past five years to evaluate the three methods of treatment. They were given information on the three treatments and then completed a self-administered questionnaire. Eight of 9 women ranked surgery as their first choice for management of a miscarriage; 1 of the 9 women preferred expectant management. The most common reasons given for the preference for surgery were wanting to have the miscarriage completed as soon as possible and wanting to avoid the extra visits to the doctor required with medical and expectant treatment. The median length of time that women reported they would be willing to wait from beginning of treatment to completion of the miscarriage was 2 days. All women chose the treatment they had received for their last miscarriage. Our results indicate that women in our study population prefer surgical treatment after a missed abortion. Factors which may lead to this choice are a low tolerance for waiting for completion of the miscarriage and familiarity with a D&C.

Oncology

ON1

K-*RAS* MUTATION DETECTED IN PLASMA DNA OF PATIENTS WITH PANCREATIC ADENOCARCINOMA. K. Pavenski*[ab], G. Liu[d], S. Narod[d], G. Lal[bc], M. Redston[b], and S. Gallinger[abc]. [a]Institute of Medical Sciences, University of Toronto, Toronto; [b]Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto; [c]Department of Surgery, Mount Sinai Hospital, Toronto; [d]Centre for Research in Women's Health, Women's College Hospital, Toronto.

Most pancreatic cancers are incurable at the time of diagnosis. This is attributable in part to a paucity of diagnostic tests that would allow early detection. Mutations of the K-*ras* oncogene are found in 75-100% of pancreatic adenocarcinomas, and 95% of these are present in codon 12. Furthermore, these mutations are acquired early in the process of oncogenesis. Hence, K-*ras* is an attractive candidate for molecular-based screening tests for pancreatic cancer. The purpose of this study is to establish a reliable and sensitive method for detection of K-*ras* codon 12 mutations in DNA derived from the plasma of pancreatic cancer patients. The method can potentially provide a minimally invasive diagnostic tool not only to aid in early diagnosis, but also to screen high risk individuals for tumor development. DNA was extracted from plasma of 45 patients with histopathologically confirmed pancreatic adenocarcinoma. Mutations in codon 12 of the K-*ras* gene were identified by a modified polymerase chain reaction procedure based on mismatched primers followed by restriction endonuclease digestion. The nature of the mutations is being determined by direct sequencing. DNA was extracted from 45 plasma samples. Preliminary analysis of 15 samples revealed 13 mutants. The mutations detected in plasma DNA were identical to those in DNA extracted from tumor tissue. Further work is ongoing to determine the sensitivity and reproducibility of the technique and its utility as a diagnostic and screening test.

ON2

SYMPTOMS AND THEIR RELATIONSHIP TO DISABILITY FOLLOWING TREATMENT FOR LOWER EXTREMITY TUMORS. Punnyamoorthy S *, Griffin AM, Wunder JS, & Bell RS, Davis AM Mount Sinai Hospital, University of Toronto

There is a paucity of information about the type and frequency of symptoms experienced by lower extremity tumor patients following treatment. The relationship of symptoms to disability has not been evaluated. This study determined: 1) the symptoms experienced by patients; 2) the change in symptoms over time: and, 3) the relationship of symptoms to disability during the early post-operative phase (6 weeks) and at recovery plateau (1 year post-surgery). At 6 weeks, 3, 6 and 12 months post surgery, 97 consecutive patients completed a questionnaire describing the symptoms they experienced in relation to their lower extremity. Disability scores were determined using the Toronto Extremity Salvage Score (TESS). Frequencies were calculated for the various reported symptoms and the Cochran test was used to determine if the frequency changed over time. Regression analysis was used to evaluate the relationship of symptoms to disability at 6 weeks and 1 year post-surgery. Symptoms significant at the p= 0.05 level in univariate analysis were evaluated in a multivariate model. 80 of 97 patients had complete symptom data for all time points. The mean age was 43.0, sd 20.4 with a gender ratio of 1:1. The symptoms reported included pain, stiffness, fatigue, weakness, limited motion at a joint, and swelling. 73 (91%) subjects experienced a least one symptom at 6 weeks. This frequency decreased over time: 68 (85%), 63 (79%) and 59 (74%) at 3, 6 and 12 months respectively. The most frequently reported symptoms were stiffness 48 (60%), weakness 41 (51%), fatigue 26 (33%), and pain 25 (31%) at 6 weeks. Stiffness and fatigue decreased and plateaued by 3 months. Complaints of weakness continued to decrease to 40 (50%), 29 (36%), and 23 (29%) at 3, 6, and 12 months. There was a slight increase in complaints of pain at 3 months, 23 (35%), which then decreased to 21 (26%) and 16 (20%) over time. Only stiffness and weakness had statistically significant changes in frequency over time. At 6 weeks, pain, stiffness, weakness and limited motion predicated disability in both univariate and multivariate analyses. At 12 months, pain, stiffness, fatigue and limited motion were significant predictors of the TESS in univariate analysis. Only pain, stiffness and limited motion remained significant predictors in the multivariate model. Pain, stiffness, fatigue, weakness and limited motion are common symptoms with stiffness and weakness decreasing significantly over time. The symptoms predictive of disability differ between the acute and late phase.

ON3

WHOLE BRAIN RADIOTHERAPY IN THE MANAGEMENT OF PRIMARY CNS LYMPHOMA IS ASSOCIATED WITH GOOD LOCAL CONTROL BUT SHORT SURVIVAL AND DELAYED NEUROLOGICAL TOXICITY. **J. Grynspan*, R. Buckstein, P. Davey, R. Farb, B. Ordonez-Perez, K. Imrie. Toronto Sunnybrook Regional Cancer Centre, Toronto, Ontario.**

We retrospectively analyzed data on 24 consecutive HIV negative patients with primary CNS lymphoma (PCNSL) treated at our institution over the last 12 years with whole brain radiotherapy (WBRT) alone. Data and follow-up information was extracted by chart review, the review of archived CT/MRI scans by a single neuroradiologist and telephone/questionnaire contact with family and surviving patients. **Results:** There were 13 males and 11 females with a mean age at diagnosis of 62 (39-84). The median dose of radiation was 50 Gy (30-64.8). 8 patients (33%) received 50 Gy in 25 fractions, 7 (29%) received a hyperfractionated regimen of 64.8 Gy in 54 fractions and 9 (38%) patients received less than 40 Gy. 14 (58%) achieved CR and 9(37%) achieved PR radiographically. Median follow-up of surviving patients was 28 months (11-43). Median overall survival was 25months (95% CI 17-33). Median DFS was 25 months (95% CI 21-29. Hypoattenuation of white matter and cerebral atrophy was seen in 10/12 patients on serial CT scans at a minimum of 6 months following completion of WBRT. Log rank analysis of baseline characteristics revealed age < 60 to be the only prognostic factor (Med. OS 38 vs. 21 months, $p<0.05$). Radiation dose, number of lesions and clinical presentation were not prognostic. **Conclusion:** Whole brain radiotherapy is extremely effective in inducing early tumour regression and transiently improving neurologic function for patients with PCNSL. Nevertheless, the mortality rate associated with delayed neurological toxicity approaches that seen upon disease relapse, and highlights important limitations of WBRT. Methods of delivery that might decrease neurologic toxicity should be explored.

ON4

OUTCOME OF OVARIAN CANCER ACCORDING TO BRCA1/2 CARRIER STATUS: A PILOT STUDY. Ha V*, Abraham R, McLaughlin JR, Narod S, Rosen B
Department of Gynecological Oncology, The Toronto Hospital - General Division, University of Toronto, Canada

INTRODUCTION

Ovarian carcinoma is the commonest cause of death from gynecological cancer. Germ line mutations of BRCA1/2 predispose women to developing ovarian cancer. There is conflicting information about the relationship between BRCA1/2 and survival. Ovarian cancers associated with BRCA1/2 mutations may have clinical and pathological features distinct from sporadic cancers. This study examines the importance of BRCA1/2 mutations in determining outcome.

PATIENTS AND METHODS

A feasibility study was done to determine whether parameters of interest were available through chart review in two Ontario centres. Patients from a previous population based 1995-97 study were selected to review. Information collected included: ovulatory history, primary therapy, prognostic factors, and progression free survival (PFS). BRCA1/2 status was already determined from the previous study. Nineteen patients were BRCA1/2 positive. Survival analysis was calculated by method of Kaplan Meier and survival experience compared using the log rank test.

RESULTS

Median age of 175 participants was 58 years (range = 20 – 87 years). Tumor grade: 14% grade 1, 31% grade 2, 40% grade 3, 6% borderline tumors, 9% unknown. Stage: 22% stage 1, 7% stage 2, 59% stage 3, 12% stage 4. Histology: 62% serous. Median PFS: 21 +/- 3 mos. Median PFS in BRCA1/2 carriers: 15 +/- 9 mos., non-carriers: 21 +/- 3 mos. ($p = 0.88$ by log-rank test).

CONCLUSION

No difference was found in progression free survival according to BRCA1/2 status. An ongoing population based study that expands on the data collected by this feasibility study will be performed to fully ascertain the importance of BRCA1/2 status as a prognostic indicator of ovarian cancer outcome, in addition to the modifying the effects of ovulatory and reproductive history.

ON5

ESTABLISHMENT OF AN ADENOVIRAL-p53 TARGETING SYSTEM IN CULTURED HUMAN OSTEOSARCOMA. P.P.C. Wong*, M. Krishnamoorthy, D. Malkin. Division of Hematology/ Oncology, Hospital for Sick Children, and Department of Medical Biophysics, Faculty of Medicine, University of Toronto.

Osteosarcoma is the second most common type of primary malignant bone tumor, reaching its peak frequency in adolescence. Despite advances in surgical techniques and the use of multi-agent chemotherapy, no curative treatment for metastatic or recurrent disease exists. Up to 50% of primary osteosarcomas harbor somatic alterations of the p53 tumor suppressor gene. p53 regulates the G1/S checkpoint of the cell cycle by monitoring genome stability and preventing replication of damaged DNA. Loss of p53 function prevents cell cycle arrest and induction of apoptosis in response to DNA damage. *In vitro* studies suggest that reconstitution of wild-type p53 in various tumor cell types that lack normal p53 function results in an induction of apoptosis and an inhibition of cell proliferation. This project involves studying the effect of *in vitro* p53 gene transfer via a replication-deficient adenovirus on 3 human osteosarcoma cell lines (KHOS, MG63, and Saos-2). Immunoblotting of lysates prepared from cell lines indicates the presence of p53 protein in KHOS, but not MG63 or Saos-2. Data will also be presented that assess the status of p53 DNA sequence, and mRNA expression at baseline in these lines. Following adenoviral infection, the effect on osteosarcoma cell growth suppression and apoptosis will be assessed. The characterization of p53 in non-infected and infected cells will form the basis for development of future *in vivo* studies.

ON6

A ROLE FOR THE PROTO-ONCOPROTEIN CBL IN HUMAN LEUKEMIA, F. Billia, J. Squire and D.L. Barber, Ontario Cancer Institute, Faculty of Medicine, University of Toronto, Toronto, Canada, M5G 2M9.

Human leukemias result from the deregulated growth of hemopoietic cells within the bone marrow. This uncontrolled proliferation can result from oncogene activation, chromosomal translocations and/or deletions. The proto-protein Cbl, which was initially described in a murine B/myeloid leukemia, appears to have at least two distinct signaling functions. It is tyrosine phosphorylated in response to growth factor receptor activation and its phosphotyrosine binding domain can downregulate tyrosine kinase activity through direct binding to activated growth factor receptors and cytoplasmic tyrosine kinases. Therefore, Cbl is considered to be a critical intracellular adaptor protein capable of regulating the assembly and activity of signaling complexes. Cbl also maps to 11q23, a common locus for genetic abnormalities in hematological malignancy. To define a role for cbl in human leukemia, the level of protein expression of cbl in various hemopoietic and leukemia cell lines was examined. In addition, fluorescence in situ hybridization for Cbl was performed in leukemia samples from with 11q23 deletions.

Cell lysates from various hemopoietic and patient-derived acute myeloid leukemic (AML) cell lines were screened for the expression of Cbl and some of its interaction partners, crkI/II and crkL by Western blot analysis. All hemopoietic cell lines examined expressed these proteins. Interestingly, the cell line AML-1 expressed significantly lower levels of Cbl, but not crkI/II or crkL as compared to three other AML cell lines. These results support a possible role for Cbl in leukemogenesis, in that removal of Cbl's negative influence in this patient's bone marrow could lead to uncontrolled proliferation and therefore leukemia. Several genes that participate in human leukemia map to chromosome 11q23 including MLL and PLZF. Bacterial artifical chromosome probes were prepared for MLL, PLZF and Cbl and fluorescence *in situ* hybridization was performed on leukemic patient samples whose primary cytogenetic abnormality was defined to be 11q23 deletions. Results of these experiments will be presented.

ON7

H-RYK RECEPTOR EXPRESSION IN BLOOD VESSELS IS A NEW PROGNOSTIC FACTOR IN EPITHELIAL OVARIAN CANCER. R.M.T. Katso, H. Ganjavi*, E. Trivier, S. Manek, M. Wells, F.M.L. Charnock, T.S. Ganesan. ICRF Molecular Oncology Laboratories, John Radcliffe Hospital, Headington, Oxford, UK and Department of Pathology, University of Sheffield Medical School, Sheffield, UK.

H.Ryk, a novel receptor tyrosine kinase is catalytically inactive and encodes for a 100 kD protein. We examined the expression of H-Ryk in normal tissues and 89 primary malignant ovarian tumours (29 serous, 11 mucinous, 29 endometrioid, 13 clear cell and 7 others) by immunohistochemistry. The receptor is expressed in epithelium of normal tissues, stroma and blood vessels (+/++/+++). Maximal expression (+++) was observed in the stroma (18/89), epithelium (22/89) and blood vessels (18/89). A detailed analysis was performed on the clinical data set of 89 patients diagnosed between 1990 and 1992. By univariate analysis (logrank test), age ($p=0.01$), stage ($p=0.0001$), residual disease ($p=0.0001$) and expression of H-Ryk in blood vessels ($p=0.03$) were significant for overall survival. Multivariate analysis (Cox regression model) showed that stage ($p=0.025$) and residual disease ($p=0.001$) were independent prognostic factors for poor survival. Expression of H-Ryk in blood vessels was significant ($p=0.05$) and predicted for poor survival. Analysis of the same tumours by immunostaining with anti-CD31 suggests that H-Ryk is not expressed in all blood vessels. Further, stable transfectants of the receptor in NIH3T3 cells are transforming *in vitro* and demonstrate increased tumourogenicity in nude mice. This implies that the expression of H-Ryk in blood vessels may reflect its role in the pathogenesis of ovarian cancer.

Ophthalmology

OP1

REDUCTION OF MONOCULAR OPTOKINETIC ASYMMETRY IN EARLY-ONSET ESOTROPIA AS CORRELATED WITH INCREASING AGE.
A.Golshan*, C.A.Westall. Visual Electrophysiology Unit, Department of Ophthalmology, The Hospital for Sick Children, University of Toronto.

Under normal binocular viewing conditions, the object of regard falls simultaneously on the fovea of each eye. The development of binocular single vision (comprised of sensory fusion and stereopsis) in infants is accompanied by the development of oculo-motor systems which function to keep the eyes aligned together. If any deviation from normal ocular alignment occurs, a condition known as strabismus results. Early-onset esotropia (inward eye turn occurring before 6 months of age) is a common clinical disorder with a prevalence of 0.09-0.5% and is associated with abnormal eye movement development and disruption of binocular function. The involuntary following eye movement reflex known as optokinetic nystagmus (OKN) is abnormal in early-onset estropia. The monocular response has been found to be asymmetric. The purpose of this study was to investigate the relationship between age and OKN asymmetry ratios. Do adaptive processes during childhood help normalize OKN asymmetry and if so, is the normalization of OKN asymmetry linked to a greater ability to control residual esotropia? Subjects tested were children with early-onset esotropia (3-12 years old) and children without esotropia (3-12 years old) who provided control data. The stimulus for OKN was a horizontally moving (20 and 30 deg/sec), 100% contrast, black-and-white vertical square wave grating, viewed monocularly on a computer screen. Eye movements were recorded by electro-oculography. Two silver-silver electrodes were placed bitemporally and the signal was digitized and analyzed Our objectives were to compare an OKN asymmetry index in children (>3 years) with early-onset esotropia with an OKN asymmetry index previously recorded in a population of infants (<3 years) with early-onset esotropia. This helped us to determine whether or not OKN asymmetry indexes did in fact decline with increasing age as studied longitudinally. Determining which children show adaptive changes to OKN will allow us to use an OKN asymmetry index as a prognostic factor in early-onset esotropia. Results thus far are showing the trends which we had hypothesized This is however an ongoing study, and further testing and data is necessary for definitive conclusions.

OP2

MOLECULAR CHARACTERIZATION OF A FAMILY AFFECTED BY HYPERFERRITINEMIA-CATARACT SYNDROME
K. McReelis*, F. Munier, G. Billingsley, E. Heon. Eye Research Institute of Canada, Toronto Hospital, University of Toronto, Canada M5T 2S8

Purpose: We report the identification and preliminary characterization of a large Swiss-Italian family affected with an autosomal dominant form of cataract that is associated with high levels of ferritin in the absence of total body iron overload. This condition has recently been identified as Hyperferritinemia-Cataract Syndrome (HCS), and the disease causing mutations are believed to occur in an mRNA hairpin known as the Iron Responsive Element (IRE). This has been shown to be contained in the 5'-untranslated region of the l-ferritin gene on the long arm of chromosome 19. Analysis of a large pedigree with affected and unaffected individuals will assist in the understanding of the pathobiology of lenticular opacification seen in HCS, which may also prove useful in the understanding of senile cataract genesis. **Methods:** Levels of ferritin for affected and unaffected members of the kindred were assessed in addition to slit lamp examination of the lens for opacity. Linkage studies were performed on affected and unaffected family members using recombinant polymorphic markers on chromosome 19. Single Strand Conformation Polymorphism (SSCP) analysis of PCR amplicons that include the IRE have been performed. Sequencing of the IRE is underway to determine the mutations responsible in this family. **Results**: An unpaired t-test of affected vs. non affected individuals ferritin levels reveals a two tailed p value of 0.004. Linkage analysis shows disease segregation over a 15 cM region on chromosome 19q13.3 between markers D19S178 and D19S601. SSCP analysis showed no significant shifts between affected and unaffected individuals.

OP3

OUTCOME OF CORNEAL TRANSPLANTS. M. Sit*, D. Weisbrod, J.Naor, A. Slomovic. Department of Ophthalmology, The Toronto Hospital-Western Division, University of Toronto, Canada.

Full thickness corneal transplantation (penetrating keratoplasty—PKP) has become a very common surgical procedure, with more than 44 000 corneal transplants performed in the United States in 1995.

Purpose: The objective of this study was to determine the graft survival rates of penetrating keratoplasty by diagnostic category.

Method: This study involved a retrospective chart review of 703 cases of penetrating keratoplasty performed and followed-up by a single surgeon at the Toronto Hospital—Western Division over a 7.5 year period (1986-June 1993). The outcome of each case was noted for up to 60 months. Primary graft failure was defined as a graft that never cleared after surgery. Secondary graft failure was the outcome of interest and this was defined as an irreversible change in the graft preventing recovery of useful vision after the graft was initially clear. Graft survival curves were determined by the Kaplan-Meier product limit method which is calculated with allowance for incomplete follow-up.

Results:

Main indication	*2 year survival (%)*	*5 year survival(%)*
Keratoconus	96	93
Interstitial keratitis	100	100
Fuch's dystrophy	88	83
Other corneal dystrophies	90	87
Herpes simplex keratitis	83	65
Pseudophakic bullous keratopathy	69	47
Aphakic bullous keratopathy	76	52
Overall	74	58

Conclusions: In our analysis, the outcome of PKP was found to be in general agreement with studies done in Australia and Europe. The original diagnosis does seem to have a predictive role on graft survival.

Otolaryngology

OT1

THE CONTROVERSIAL USE OF AND THE BENEFITS ACCRUED BY COCHLEAR IMPLANTS.

Stacey Shapira*, Sharon M. Abel. Department of Otolaryngology, University of Toronto, Canada.

Background: Over the last century, advances in rehabilitation technology have lead to improvement in auditory perception and communication in hearing-impaired individuals. The newest technology is the Cochlear Implant (CI). However, the use of CIs is controversial. The hearing community views deafness as a medical pathology in need of repair. The deaf community feels that it is futile to fix something that isn't broken. ***Objectives***: The purpose of this study was two-fold: firstly, to address the varying attitudes towards CIs within and between the deaf and hearing cultures, and secondly, to determine the benefits accrued by the use of a CI with respect to spatial hearing. ***Methods***: A 26 item Attitudes Survey was developed. Each question was in the form of a 5-point Likert scale. Twenty-two deaf individuals completed the questionnaire: 12 who did not use a CI (7who had deaf children and 5 with no deaf children), and 10 who were fitted with CIs and had demonstrated benefit in speech understanding. A sound localization experiment was conducted in the hearing research laboratory at Mount Sinai Hospital. ***Results***: The Attitudes Survey indicated polarization in views between deaf and hearing individuals with respect to deafness as a medical pathology, the use of CIs for enrichment of life, and the integration of CI individuals into the Deaf or Hearing cultures. Unaided deaf were divided in terms of perceived benefits of the CIs. The localization study showed no overall benefit in spatial hearing,although there are wide differences in outcomes. ***Conclusions***: The Attitudes Survey showed that unaided deaf parents would benefit from education on CIs. As well, the hearing community should be educated on the capabilities of the deaf and their health needs. The sound localization study suggested that the benefits of CIs are limited to enhanced communication and thus new technology should focus on improving other auditory abilities. Further investigation must be pursued to determine the factors which predispose some implanted individuals to have better spatial hearing.

Pediatrics

PE1

EVALUATION OF THE CHILD HEALTH QUESTIONNAIRE. K. Dang*, W.A. Khan, N.L. Young, J. Friedman. Division of Paediatric Medicine, The Hospital for Sick Children, University of Toronto, Canada, M5G 1X8.

Objective. To evaluate the validity and clinical responsiveness of the Child Health Questionnaire (CHQ) in a group of children with common paediatric conditions. The CHQ is a new generic measure of health for children over five years of age. CHQ scores range from 0 to 100; the higher the score, the better the health of the child.

Methods. A modified version of the CHQ was administered to parents of children over five years of age, who were admitted to the general paediatrics ward at The Hospital for Sick Children on three occasions: at hospital admission (Time 1), at discharge (Time 2), and at two weeks post-discharge (Time 3). Parents of children with asthma also completed the Paediatric Asthma Quality of Life Questionnaire (PAQLQ), a reliable and valid measure of health in children with asthma. Validity was assessed by Pearson's correlation coefficient between CHQ and PAQLQ scores at Time 1. Clinical responsiveness was assessed using an effect size and a paired t-test between Time 1 and Time 3, and using an ANOVA of the scores by diagnostic group at Time 1.

Results. Sixty-six parents completed the questionnaires at Time 1, 36 parents at Time 2, and 37 parents at Time 3. Validity was assessed using data from the asthma sub-group at Time 1 (n=14). The mean CHQ score was 54.7 (SD=12.8) and the mean PAQLQ score was 4.0 (SD=1.3), with a Pearson's correlation coefficient of 0.70 ($p=0.005$). Clinical responsiveness was assessed by the effect size between Times 1, 2 and 3. Data at Time 2 indicated worse health than at Time 1, which was contrary to our a priori hypothesis, and thus excluded from our analysis. Using data from children at both Time 1 and Time 3 (n=37), the mean change in scores was 8.7 (SD=10.8). This yielded an effect size of 0.81, indicating a statistically significant improvement after discharge ($t=4.9$, $p<0.0001$). The ANOVA by diagnostic group was consistent with our a priori predictions. Scores for children with acute health problems were significantly higher than scores for children with exacerbations of chronic health problems ($p<0.05$).

Conclusions. The CHQ is valid in comparison to another health measure in a community, but not a hospital setting. The CHQ is responsive to clinically important change in the health of children following hospitalization for acute and chronic paediatric health problems.

PE2

THE LONG-TERM OUTCOME OF NON-ORGANIC FAILURE TO THRIVE FOLLOWING MULTIDISCIPLINARY INTERVENTION

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Little is known about the long-term growth and developmental outcome in non-organic failure to thrive (NOFTT). This study aimed to determine. 1) if the improvement in growth following outpatient multidisciplinary intervention is sustained and 2) the developmental status at follow up. Children under 3 years of age were eligible for the study once gross developmental delay, genetic syndromes or major medical problems were excluded. Of the 40 invitations mailed, 7 families participated in the study. Medical charts were reviewed for histories, serial weight and height measurements. At follow-up, medical histories and physical examinations were performed. Development was assessed directly by the Denver Developmental Screening (DDS) tool and indirectly by the Vineland Adaptive Behaviour Survey. The etiology of NOFTT of all the study participants was related to behavioural feeding problems. During the period of clinic intervention, 6 of the children advanced from weights which filled the criteria for failure to thrive (<3 percentile or falling across 2 major percentile lines) to weights which had reached the 3rd percentile mark for weight. Three of the children had improvements in percentile rankings for height. At time of follow up (0.7-2.6 yrs after clinic discharge), the children were ages 3 to 7 years. All had maintained their weights at or above the 3rd percentile. Five of the children had crossed 1 major percentile line and one child crossed 2 major percentile lines. There were no abnormalies in development detected using the DDS. The behavioural survey revealed mean standard scores for communication, daily living, socialization and motor skills that were all within the 'adequate' range. However, none of the 6 children assessed for maladaptive behaviour received a score within the 'adequate' range. An 'intermediate' score was achieved by 4 and an 'extreme' score by 2 of the 6 children indicating that compared to children the same age, they exhibit more maladaptive behaviours than 50% and 75% of children respectively. This preliminary data suggests that the success achieved in growth rates by treating NOFTT with an outpatient multidisciplinary approach is sustained in the long term. While gross abnormalities in development were not detected, there was evidence of some behavioural problems. Further data is needed to interpret the significance of these findings.

Pharmacology

PH1

COMPARISON OF ORAL VERSUS RECTAL ACETAMINOPHEN DOSING IN THE TREATMENT OF FEVER IN CHILDREN. J. Caulfeild*, D. Scolnik, S. Jacobson, N. Young, S. Diamond, et al. Divisions of Emergency Services, Clinical Pharmacology and Toxicology, Paediatrics, and Pharmacy, The Hospital for Sick Children, University of Toronto, Canada, M5G 1X8.

In North America, the standard oral dose of acetaminophen given to children is 15 mg/kg, which has proven to be very effective treatment for pain and fever. In situations in which the drug must be given by rectal suppository, the same dose of 15 mg/kg is given. Recent evidence in the literature suggests that at least twice this amount is necessary when the drug is given as a rectal suppository. To date, no controlled study has simultaneously investigated the antipyretic effect and the pharmacokinetics of both normal and increased doses of rectal acetaminophen when used in the treatment of fever in children. Thus, this study aimed to demonstrate that acetaminophen administered by rectal suppository should be given in a dose twice that of the oral form (ie. 30 mg/kg) to achieve adequate serum levels and to reduce fever in children more effectively.

Children between the ages of 6 months and 6 years who had not received acetaminophen in the previous four hours and presented with a fever $\geq 39°C$ were randomly assigned to receive one of three treatments of acetaminophen: 15 mg/kg PO, 15 mg/kg PR, or 30 mg/kg PR. The primary endpoint was change in temperature, while the secondary endpoint was the salivary levels of acetaminophen. The T-test was used to assess differences in values among the groups.

Thus far, the data from 30 patients has been analyzed, but a total of 71 patients have been recruited for this ongoing study, and final results are pending. The data from the first 30 patients shows that at the point of maximal expected action of acetaminophen, 20 minutes after dosing, 30 mg/kg PR was significantly more effective than 15 mg/kg PR in reducing temperature. Other time points showed similar trends. Area under the curve for salivary concentrations among the 3 groups did not show significant differences. Thus, preliminary results indicate that 30 mg/kg PR acetaminophen appears to be more effective in lowering fever in children than 15 mg/kg PR, the dose that is currently recommended in North America. This increased efficacy is not accompanied by significant increases in systemic concentrations of the drug.

PH2

PATIENT PERSPECTIVES ON DECISION-MAKING IN TREATMENT OF NON-HODGKIN'S LYMPHOMA. H. Chen*[1], A. Bezjak[2] and T. Bunston[3]. [1]Faculty of Medicine, University of Toronto, Toronto; [2]Department of Radiation Oncology, Princess Margaret Hospital, Toronto; and [3]Psychosocial Oncology Program, The Toronto Hospital/Princess Margaret Hospital, Toronto.

The ultimate goal of this project was to facilitate communication and decision-making about treatment alternatives for patients with non-Hodgkin's lymphoma (NHL). The purpose of this student project was to explore patients' attitudes and behaviour towards information provision and decision-making with respect to NHL treatment.

Patients with NHL seen in follow-up at Princess Margaret Hospital, Toronto, Ontario participated in the study. These patients were either stage I or II NHL at the time of diagnosis and had completed treatment (radiation, chemotherapy or both) 4 to 24 months prior to their upcoming visit. Patients were required to fill out several validated self-report questionnaires and participate in an audiotaped interview about their decision-making process. The semi-structured interview addressed the following topics: Did the patient feel s/he was given a choice of treatment, how the patient made the decision, what influenced the patient's decision and the patient's satisfaction with the decision-making process.

Seventeen patients were interviewed and transcripts were obtained. Fifteen completed questionnaires have been received to date. The interview transcripts are being reviewed independently by each investigator and themes relevant to this patient population are being determined. Preliminary results indicate that NHL patients are satisfied with the information provided to them. Most patients are only advised of the treatment option that their physician believes is medically most appropriate, and the patients have indicated that they are satisfied with this decision-making process.

Conclusions will be arrived at from the interview data along with the quantitative data from the questionnaires and charts. The data from the patients in this study need to be analyzed along with data from the parallel study examining physician's attitudes and behaviour regarding treatment decision-making. Increased knowledge on this issue will allow greater communication between patients and physicians, and may lead to improved patient compliance and satisfaction with decision-making and quality of care.

Psychiatry

PS1

THE MEASUREMENT OF MOOD LABILITY. K. Balchand*, P.S. Links. Arthur Sommer Rotenberg Chair in Suicide Studies, University of Toronto.

Lability of mood is found in some psychiatric disorders, notably borderline personality disorder, and may be associated with suicide. Mood lability can be measured by serial administration of a visual analogue mood scale (VAMS) but the need for repeated measurements makes it an inconvenient test and leads to low compliance. We examined the hypothesis that the Affective Lability Scale (ALS), which can be completed in one sitting, adequately captures mood lability. We compared ALS scores to VAMS variability scores in 16 consecutive psychiatric inpatients who were not actively psychotic. We also compared each of the two scales to self-reported suicidal behaviour using the Suicidal Behaviors Questionnaire (SBQ). Each subject completed an ALS and an SBQ, followed by one week of twice-daily VAMS measurements, and then another ALS. The ALS showed sufficient test-retest reliability but was not correlated with the VAMS mood variability scores. Both VAMS and ALS scores were generally higher in high-frequency suicidal ideators than in low-frequency ideators, although the differences were not significant. With respect to suicide attempts in the last year, those who reported a suicide attempt had higher ALS but lower VAMS variability scores than those who reported no attempts, although the differences were not statistically significant. In conclusion, the ALS does not appear to reflect mood lability. Therefore, it cannot be used instead of VAMS without a further understanding of the situations, if any, in which it is an effective measure of mood lability.

Rheumatology

RH1

Physical and Psychosocial Long-Term Outcomes of Pauciarticular Juvenile Rheumatoid Arthritis

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This study is a large-scale assessment of Juvenile Rheumatoid Arthritis (JRA) outcomes, evaluating the joint condition, vision impairment, and psychosocial effects resulting from JRA in order to define a more accurate prognosis of JRA disease course. The correlation of physician's assessment and patient's perception of health status and quality of life is also examined. A chart review of approximately 120 patients seen at the Hospital for Sick Children Rheumatology Clinic and diagnosed with pauciarticular JRA 10 or more years ago yielded 81 candidates who met the criteria of pauci involvement throughout the course of their disease. The incidence of uveitis among study candidates was 18.5 %, with females outnumbering males 3 to 2. All uveitis patients had tested positive for ANA during the course of disease; however, high ANA titers were not a predictor for uveitis. The Health Assessment Questionnaire (HAQ/CHAQ, as appropriate for each patient's age) was used to assess the patients' evaluation of their current health, disability conferred by JRA, ability to function, and overall quality of life. The SF-36 Health Survey addressed the patients' current psychosocial adjustment and well-being, as well as quality of life. Supplementary questions were asked to determine the patients' current social status. The physician's evaluation of patient's function included a detailed interview, followed by thorough physical examination, blood work, and radiographic assessment. Preliminary results indicate that the previously accepted dogma of 80 % recovery at 5 - 10 years post-diagnosis may be unduly optimistic. As many as 40 % of the patients seen to date have joint symptoms. Leg length discrepancy, one of the complications of JRA, was found to persist in 20 % of the patients examined. On the psychosocial front, only a minority of patients seen have reported depression, while virtually all patients stated that JRA has not interfered with their social adjustment.

RH2

COMPARISON OF RADIOGRAPHIC FEATURES AND SEVERITY IN PSORIATIC ARTHRITIS (PSA) AND RHEUMATOID ARTHRITIS (RA)

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Objective: To determine if there are differences in radiographic severity between PsA and RA and to identify radiographic features which distinguish PsA from RA. ***Methods:*** Plain radiographs of hands, feet and cervical spine were collected for RA patients. PsA patients were matched to the RA patients according to gender, age and disease duration at the time the radiographs were performed. The earliest radiographs for each patient were presented randomly to two rheumatologists who were blinded to the patient's diagnosis and other identifying information. A modified Steinbrocker classification was used to assess the degree of joint damage in the hands and feet. Other radiographic findings not included in the modified Steinbrocker classification were recorded for radiographs of the hands, feet and cervical spine. A matched analysis using paired t-tests was performed to compare severity in RA and PsA. McNemar's test was used to compare the frequency of radiographic features in RA and PsA. ***Results.*** The study population comprised of 66 females and 18 males. The mean age and mean disease duration were 53.0 years and 6.1 years respectively for the RA patients and 53.2 years and 6.9 years respectively for the PsA patients. The overall Steinbrocker score was similar in both patient groups ($p=0.32$). However, RA patients demonstrated a greater degree of severity in the feet than patients with PsA ($p=0.026$). A trend was observed for the presence of fluffy periostitis, bony proliferation and dactylitis in the hands, calcaneal spurs in the feet, syndesmophytes in the cervical spine in PsA patients. RA patients had a higher frequency of joint space narrowing without erosion in the hands, and atlantoaxial subluxation and intervertebral disc space narrowing in the cervical spine. ***Conclusion.*** There is no overall difference in radiological severity in patients with RA compared to PsA, although patients with RA have more severe changes in their feet. New bone formation and dactylitis were the radiographic features that distinguished PsA from RA. Perhaps a new radiographic classification needs to be developed to account for these differences in radiographic features and severity between RA and PsA.

SU1

DOWN-REGULATION OF T-CELL RESPONSE BY HUMAN-FAS LIGAND TRANSFECTED DENDRITIC CELLS. C Rowsell*, W-P Min,X Huang, R Gorczynski, MS Cattral Multiorgan Transplantation Programme, Department of Surgery, University of Toronto, Canada, M5G 2C4.

Genetic modulation of dendritic cells (DC) by transfection of immunoregulatory genes is a potential approach for inducing tolerance. We evaluated the effect of transfecting Fas ligand (FasL) on the stimulatory capacity of bone marrow-derived DC. DC were generated from murine bone marrow cultured with GM-CSF and IL-4. Whole-length human FasL (membrane-form, mFasL) and a truncated form of FasL (secretory form, sFasL) were subcloned into a mammalian expression vector under the control of CMV promoter. Both constructs were also inserted into a replication-deficient adenoviral vector (Adv). Gene expression was determined by RT-PCR, FACS, and function was assessed by killing of a Fas+ cell line 48 hours after transfection. The stimulatory capacity of FasL transfected DC (FasL-DC) was assessed by mixed lymphocyte reaction(MLR).Both DNA constructs were successfully transfected into COS-7 cells and DC with lipofectin and Adv. Supernatants from sFasL transfected COS cells induced apoptosis of the Fas+ cell line. Expression of FasL in DC was confirmed by RT-PCR and by FACS. FasL-DC induced apoptosis of the Fas+ cell line, and significantly inhibited T cell proliferation in MLR. Conclusion: DC can be transfected with FasL by either liposomal and Adv gene delivery methods. Allogeneic T cell responses are decreased after coculture with DC transfected with FasL. These findings suggest that induction tolerance by transfusion of genetically engineered DCs in allograft recipients may be possible.

SU2

MISSED INJURIES IN MULTIPLE TRAUMA PATIENTS. G. Buduhan*, D.I. McRitchie. The Department of Surgery and the Cara Phelan Centre for Trauma Research, St. Michael's Hospital and the University of Toronto, Toronto, Canada.

Background: Multiply injured trauma patients pose unique challenges in diagnosis and management. Many factors may contribute to the frequency of missed injuries in this population. The purpose of this study was to determine the incidence, contributing factors and clinical outcomes of missed injuries in a Canadian Level I Trauma Centre.

Methods: Using a database of all patients assessed by the trauma team and admitted to St. Michael's Hospital from April 1995 to July 1997, 567 patient records were examined and 46 patients with missed injuries were identified. Independent chart reviews of the missed injury population were conducted to identify risk factors, patterns, clinical outcomes and factors contributing to delayed or missed diagnoses.

Results: Patients with missed injuries were found to have higher mean Injury Severity Scores and longer hospital and ICU length of stays, when compared to trauma patients without missed injuries ($p<0.05$). Missed injury patients were also more likely to have lower initial GCS scores and to have required pharmacologic paralysis in the resuscitation room ($p<0.05$). The most common anatomic sites for missed injuries were the limbs (33.3%), head (30.2%) and thorax (19.1%). Fifty-four percent of missed injuries involved the musculoskeletal system, whereas 23.8% were neurologic. Forty of 46 patients (87.0%) had no significant sequelae of their missed injuries. Seven patients had clinically significant sequelae as a direct result of delayed diagnosis, including 1 patient death. Of the factors contributing to missed injuries, 56.3% were deemed to be potentially avoidable; 43.8% were classified as unavoidable. Of the potentially avoidable factors, inadequate clinical assessment was a contributing factor in 33.8%. The most common unavoidable factor was an altered level of consciousness (17.5%), followed by delayed presentation (16.3%). Of the 7 clinically significant missed injuries, 5 were due to potentially avoidable factors.

Conclusions: A small yet significant proportion (8.0%) of injuries are missed in multiple trauma patients. Those with missed injuries tend to be more severely injured or have other impediments to accurate clinical assessment. Many of these missed injuries are avoidable with complete, thorough assessment and a high degree of clinical suspicion. Fortunately the vast majority (87.0%) have no clinical sequelae.

SU3

Investigation of lipopolysaccharide (LPS) levels and a systemic inflammatory response in patients undergoing elective or rupture abdominal aortic aneurysm (AAA) repair. J. Stewart*, P. Midgley, T.F. Lindsay. Division of Vascular Surgery, The Toronto Hospital, University of Toronto, Canada, M5G 2C4

Shock caused by rupture and lower torso ischemia during repair may cause release of LPS into the systemic circulation potentiating an inflammatory response. This release may contribute to multiple organ failure, and the increased morbidity and mortality evident in ruptured AAA repairs compared to elective AAA repairs. We wished to determine if there was evidence of LPS release into the systemic circulation following elective and ruptured AAA repair.

The LPS receptor (CD14) binds LPS to the cell surface, upregulating its transcription and enabling removal of LPS from the circulation. LPS also causes release of TNF-α which stimulates neutrophil activation. Initially, CD120a (TNF receptor) downregulates in the presence of TNF-α, allowing accumulation of TNF in the circulation. Eventually CD120a is upregulated, but TNF-α may already be effecting a systemic response.

Blood samples were obtained from patients undergoing AAA repair (elective and ruptured) at perioperative time points. Samples were analyzed for LPS, CD14 and CD120a expression, and neutrophil oxidant and phagocyte production. Some plasma was frozen for limulus amebocyte lysate (LAL) assays (LPS gold standard) at a later date. Clinical data was collected for correlation to experimental data.

Ten elective patients and one ruptured patient were sampled. Significant changes include: increases in phagocyte count between pre-incision (PI) (4130±358) and pre-clamp release (PR) (5070±661) compared to post-clamp release samples ($p<0.005$ and $p<0.05$ respectively); granulocyte CD120a decreases from PI (2.56±0.07) to the 4hr. post-release (4PR) sample (2.16±0.08, $p<0.001$), then increases postoperatively (D3, 2.43±0.08, $p<0.05$); granulocyte CD14 decreases from PI (2.96±0.14) to 4PR (2.53±0.12, $p<0.05$), then increases 1 day postoperatively (2.87±0.14, $p<0.05$); monocyte CD120a increases from PI (2.03±0.05) to day 1 (2.30±0.07, $p<0.05$) then continues to increase to day 3.

Although a significant change in LPS concentration was not evident, receptor changes were consistent with LPS release. Further LAL and TNF assays will define LPS levels.

SU4

SURGICAL VERSUS TRANSCATHETER DEVICE CLOSURE OF SECUNDUM ATRIAL SEPTAL DEFECTS—A CLINICAL DECISION ANALYSIS

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Background. As there have been no randomized controlled trials comparing surgical (SURG) vs. transcatheter device (CATH) closure of uncomplicated secundum atrial septal defects (ASD), controversy continues as to which option has the more preferred overall outcome.

Methods. We reviewed the contemporary literature and identified 21 case series describing 881 SURG and 501 CATH procedures. From meta-analysis, a decision tree was created with 33 combinations of outcomes, including completion of the intended procedure and cross-overs, minor and major complications and residual defects. Probabilities were derived for each combination of outcomes. Preferences for these outcomes (utilities; 0=certain death, 1=perfect outcome) were derived from a modified standard gamble interview of 17 cardiology fellows, 15 clinical epidemiology students, 5 cardiologists, 4 cardiac surgical fellows, 4 cardiac surgeons, and 3 nurses (n=48). Results relate to a procedure for an uncomplicated ASD in a 2 to 18 year old. Final utilities for each decision were compared.

Results. Estimated mortality related to CATH vs. SURG was not significantly different ($p=0.10$). Initial preference was for CATH in 40, SURG in 7 and indifferent in 1 subject. After clinical decision analysis, final mean utilities favored SURG (0.9967 ± 0.0060) vs. CATH (0.9916 ± 0.0100, $p<0.0001$), with higher final utilities for SURG in 40, CATH in 6 and no difference in 2 subjects. SURG was preferred in all groups of subjects. In sensitivity analysis, CATH would be favored only if the probability of successful device implantation approached 100% together with a probability of residual shunt near 0%.

Conclusion. While there was an initial bias towards CATH, systematic assessment by clinical decision analysis showed SURG to be the preferred option for closure of uncomplicated secundum ASD.

SU5

DELAYED NEONATAL DEATHS: AN ANALYSIS OF THE MAGNITUDE AND IMPACT OF THE PROBLEM. D.A. Weizman*, N.E. Wiseman, A.A. Abdoh. Department of Surgery, Faculty of Medicine, University of Manitoba, Winnipeg Children's Hospital, Winnipeg, Canada R3A 1S1.

The increased medical efforts directed towards rescuing tiny premature infants has resulted in a well substantiated reduction in neonatal mortality as well as a less well characterized subset of postneonatal deaths herein termed Delayed Neonatal Deaths (DND). The purpose of the present study was to describe this group of patients at two major tertiary care centres and to define their impact with respect to medical resource utilization. A chart review of all postneonatal deaths (1986-1997) was conducted for a total of 56 cases with a slight increasing trend in the number of DND during the last 5 years. Median LOS and survival time were 52.5 and 100.0 days respectively. The mean cost of care per infant was $126,863.37. Despite only a slight trend towards an increase in the incidence of DND, the DND phenomenon exists and this group of patients have a significant impact on medical resources.

SU6

THE SELF-ALIGNING KNEE SYSTEM. A FIVE TO EIGHT YEAR FOLLOW-UP STUDY. C.L. Render-Teixeira* and R.B. Bourne. Division of Orthopaedic Surgery, London Health Sciences Centre, University of Western Ontario, Canada N6A 5A5.

The effect of total knee replacement on health and functional independence measures of patients who have osteoarthritis was examined in the present study. 141 patients received 172 primary total knee replacements (31 bilateral) between January 1990 and April 1994, with insertion of the self-aligning knee (SAL). Of these, 68 patients (73 knees) have been followed for a period of 5 years or more (range 5 to 8 years, mean 5.5 years). A further 19 patients (23 knees) have died, and 13 patients (13 knees) are lost to follow-up for reasons of revision or infection. Only 1 patient (bilateral knees) refused to return for assessment. At this time there are still 33 patients who require follow-up to complete the data set and a further 7 patients who are not yet 5 years post surgery. The mean age of the patients at time of surgery was 69 years (range 47.3 to 83.9 years); 39 of the surgeries were performed on men (53.4 per cent). The patients were evaluated clinically and radiographically according to a modified version of the scoring system of the Knee Society, and also answered questions regarding patient satisfaction and level of function.

There was significant improvement in all aspects of the Knee Society score following the surgery. Many of these improvements were apparent by 6 week follow-up. The mean function and clinical scores were 74.4 and 89.7 points, respectively, at the most recent follow-up examination. The result was excellent for 36 knees, good for 34, fair for 3 and poor for none. Non progressive radiolucent lines were present at the cement bone interface in 40.2 percent of the knees that had a complete radiographic follow-up. No prosthesis had loosened by the time of the most recent follow-up. In the present study, total knee replacement with the SAL knee prosthesis resulted in excellent relief of pain, an excellent range of motion and restoration of function in patients with osteoarthritis.

SU7

HEPATITIS C VIRUS INFECTION (HCV) IS ASSOCIATED WITH A HIGH INCIDENCE OF DIABETES MELLITUS BEFORE AND AFTER LIVER TRANSPLANTATION. J Pennington*, MS Cattral. Multiorgan Transplantation Programme, University of Toronto, Canada, M5G 2C4.

Abnormalities of carbohydrate metabolism are a well-recognized complication of cirrhosis. Recent studies suggest that HCV may be a risk factor for the development of diabetes mellitus (DM). We retrospectively reviewed 207 patients who received liver transplantation (OLTx) between 1986 and 1997 to assess the influence of the primary cause of cirrhosis on the prevalence of DM before and after OLTx. The cause of cirrhosis was HCV in 89, hepatitis B virus infection (HBV) in 25, and cholestatic liver disease in 93 patients. Risk factors for DM (age, sex, body mass index (BMI), cyclosporine levels, rejection episodes and cumulative steroid dosage) were determined.

	HCV(n =89)	HBV(n = 25)	Cholestatic(n= 93)	P
Mean (±SD) age (yrs)	51±12	47±12	47±12	NS
Female	40 %	44 %	59 %	0.04
BMI	27±5	24±3	24±4	0.001
DM before OLTx				
Diet controlled	9 %	0 %	1 %	
Oral hypoglycemic	8 %	4 %	0 %	
Insulin dependent	9 %	4 %	2 %	0.001
DM 1 year after OLTx				
Diet controlled	3 %	0%	1 %	
Oral hypoglycemic	3 %	4 %	1 %	
Insulin dependent	33 %	12 %	4 %	0.0001

There were no significant differences with respect to mean cyclosporine levels and number of rejection episodes among the 3 groups. Cumulative steroid dosage during the 1st year after OLTx was significantly lower for patients with HCVand HBV than for those with cholestatic disease. **Conclusions:** HCV is associated with a marked increase in the incidence of DM both before and after OLTx. Most patients with glucose intolerance after OLTx required insulin therapy. Further studies are needed to delineate the mechanism(s) that link DM and HCV.

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